Corpus Uteri Malignancies in The Netherlands since the 1980's

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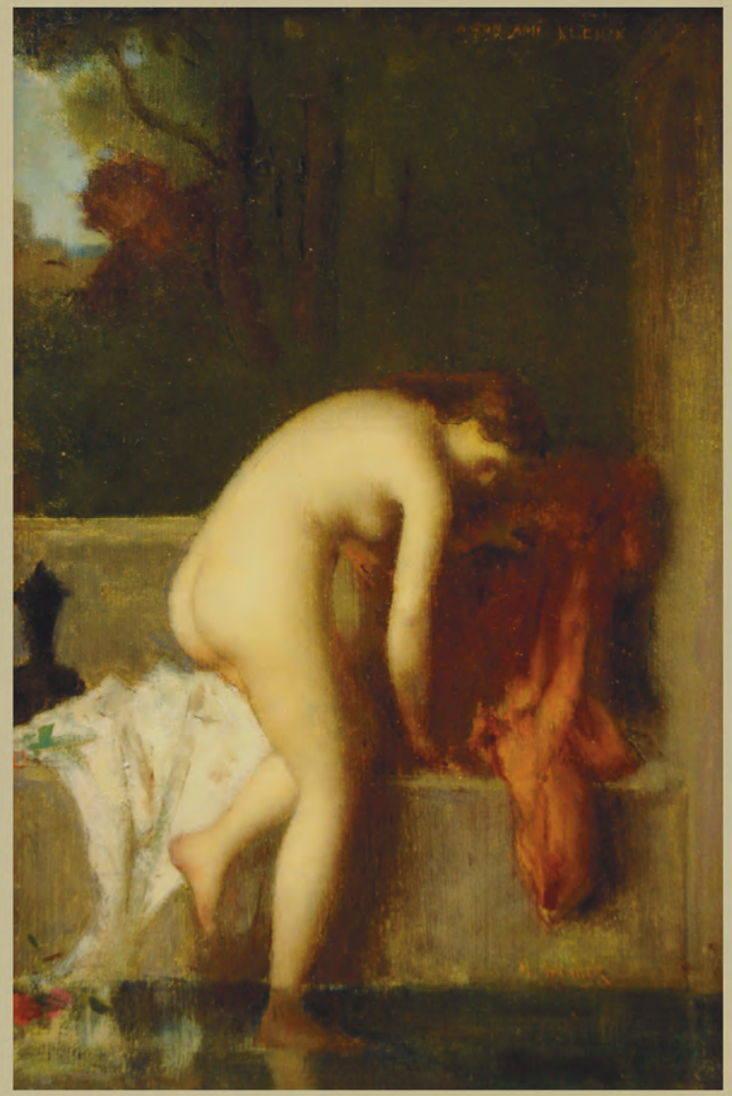
Registry-based studies of variation in incidence and outcome



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Registry-based studies of variation in incidence and outcome

Corpus uteri maligniteiten in Nederland sinds 1980

Studies naar variatie in incidentie en uitkomsten, gebaseerd op kankerregistraties

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General introduction and outline of the thesis

General introduction

This thesis provides detailed information on the epidemic of corpus uteri malignancies in the Netherlands. We present age, stage, and histology-specific trends in incidence, relative survival rates, and mortality of uterine malignancies between 1989 and 2009, with a view to assessing the progress against uterine malignancies during the past two decades.
The majority of uterine malignancies, approximately 80%, appear to be endometrioid endometrial carcinomas (EECs). The remaining 15% are non-endometrioid endometrial carcinomas (NEECs), a percentage that might possibly decrease with the improvement of pathologic classification. A minority (4%) comprised the mesenchymal corpus uteri malignancies, also referred to as sarcomas. Contrary to NEEC, EEC has a good prognosis. In these types of cancer relative survival statistics are of limited clinical relevance, because relative survival and observed survival differ. Observed survival reflects the effects of both non-cancer-related and cancer-related causes of death. Therefore, we explored the influence of patient characteristics like co-morbidity, such as diabetes mellitus, age of treatment, and survival. As progress is made, the number of EEC survivors will increase. The actual benefit of progress against uterine malignancies needs to be analysed in relation to the long-term sequelae of cancer management and the health-related quality of life (HRQoL) of cancer survivors. The number of long-term EEC survivors are expected to increase substantially, i.e. 3-5% per year. For this reason we presented a HRQoL analysis of EEC cancer survivors. Gynaecologists are having to deal with an increasing number of women with a high body mass index (BMI) who develop EEC. This called for a HRQoL analysis according to BMI, because recovery and rehabilitation of these women may be hampered.

Progress against cancer

Cancer statistics form the foundation of our ability to measure the progress against cancer. Recently, the Dutch Cancer Society funded the project "Progress against cancer in the Netherlands since the 1970s". In this study a new framework was investigated to measure the progress against cancer(1). The framework combined incidence, survival, and mortality to achieve a more objective assessment of progress against cancer. Based on these three measures progress can be: (i) decreasing incidence due to the prevalence of lower preceding risk factors or screening for premalignant lesions and (ii) improving survival rates due to changes in incidence and changes in therapy regimens. Changes in both incidence and survival affect mortality. Optimal progress is reflected by decreasing incidence and/or improving survival rates accompanied by decreasing mortality. In the aforementioned study corpus uteri cancer was classified as a tumour with optimal progress according to improved survival, but non-improver, because of the increased incidence. In Chapter 2 we describe the progress in corpus uteri cancer.

Epidemiology of malignancies of the corpus uteri

Worldwide, corpus uteri malignancy is the fifth most common cancer in women. It accounts for 4.8% of cancer in women and is the tenth cause of cancer deaths(2). In the Netherlands, corpus uteri malignancy ranks sixth in incidence after breast, colon, lung, skin cancer and melanoma. The oldest cancer registry, the Danish Cancer Registry, calculated a world standardised ratio (WSR) incidence of corpus uteri malignancy of 12.5 per 100 000 in 1998. The EUROCARE-3 and EUROCARE-4 data(3) depicted that the increasing incidence in the Netherlands until 2009 showed a estimated annual percentage change (EAPC) of 1.6 and the incidence (WSR) increased from 11 per 100 000 to 16 per 100 000 between 1989 and 2009. In Northern Ireland the increase was higher, with an EAPC of 5.5, in Lithuania the EAPC was 5.2 and in Italy, Norway, and England and Wales, the EAPC measured 2.1 to 2.5. The analyses from the databases of the National Program of Cancer Registries (NPCR) and Surveillance Epidemiology and End Results (SEER) programmes of the USA between 1999 and 2006 (covering 88% of the USA), showed the highest increases. The incidence of EEC rose from 12.5 to 22.9 per 100 000 (corrected for the standard US population) and an EAPC of 6.3(4). In the EUROCARE statistics all uterine cancers were analysed together. In the analysis of the SEER and NPCR databases EEC and the non-endometrioid endometrial carcinoma (NEEC) were analysed separately. In the USA the incidence of NEEC increased from 1.3 to 1.5 per 100 000 and an EAPC of 2.2 between 1999 until 2006. Evans(5) et al. presented data on a part of United Kingdom in which EEC increased from 12 to 16 per 100 000 (European Standardized Ratio, ESR), while NEEC decreased from 2.5 to 2.2 per 100 000 between 1994 and 2006.

Survival rates of malignancies of the corpus uteri

Relative survival in the patient group under consideration is defined as the ratio of the observed survival rate to the expected survival rate in a group taken from the general population, with similarity in both groups for age, sex, and calendar time(6). Thus the observed survival rate, taking into account all causes of death, is always less than relative survival. In the case of malignancies associated with high lethality's, like the NEEC tumours or sarcomas, there may be little difference between observed and relative survival rates. In cancers with good prognoses like EEC the relative survival rate and observed survival ratios differ more due to the greater probability of deaths from other causes. This effect is more pronounced in older patients and patients with co-morbidity.

The overall relative five-year survival rates (RS) reported in the literature lies between 68% and 84% in the period from 1990 to 2010. In the FIGO Annual Report(7) a five- year RS of 80% was reported for corpus uteri cancer from 1999 to 2001. The data from Norway(8) showed a five-year RS of 77.8% from 2000 to 2010 and a disease- specific five-year survival of 86.9%. The SEER data reported a five- year RS of 79% from 1992 to 2004 and an observed survival rate of 76%(9). The Netherlands Cancer Registry (NCR) data showed a five-year RS of 80% between 2007 and 2009(1). In the UK the overall five-year RS was 76% for corpus

uteri malignancies, for EEC the five-year RS was 82%, and for NEEC it was 41% from 1999 to 2003(5).

Mortality

In the developed world cancer of the corpus uteri is the third cause of death due to gynaecological cancer after ovarian and cervical cancer(10). In the Netherlands, corpus uteri malignancy ranks eleventh in cancer mortality after breast, colon, lung, and skin cancer and melanoma and it is the second cause of death in gynaecological cancer. Mortality rates are influenced by both incidence and survival and reflect the risk of cancer-related deaths among patients diagnosed over the preceding years. Mortality statistics are based on the registration of cause of death, which has its problems in terms of reliability. In the Netherlands the reliability of coding the cause of death for the major causes of death is high (>90%)(11). The mortality rates reported in the EUROCARE studies are ratio's (WSR) for Northern and Western Europe of between 1.1 and 2.8 per 100 000 between 1994 and 2009(3). The EAPC varies between -3.5 and -0.1 and was only significant for France. In Southern and Central Europe, i.e. Spain, Poland, Slovenia and Croatia, mortality declined significantly.

Tumour characteristics

Classification

The classification of corpus uteri malignancies is divided into epithelial malignancies (carcinomas) and mesenchymal malignancies (sarcomas) (Table 1).

History of histopathological diagnosis and molecular biology in corpus uteri diagnosis

The development of immunohistochemistry and molecular genetic studies have had an important influence on the increase in differentiating corpus uteri malignancies. Many changes in the definitions of the different histopathological diagnoses in epithelial tumours took place between 1982 and 1994(14), in mixed mesodermal tumours(15) between 1997 and 2000, and in the sarcomas between 2000 and 2004(16;17). In the 2002 edition of Blaustein's pathology of the female tract 20 different histopathological diagnoses are given on epithelial endometrial carcinoma alone(12). Clement and Young even described 23 histological types(18).

In 1983, Bokhman(19) classified epithelial endometrial carcinomas into two types: Type I, oestrogen-related carcinomas, are usually associated with endometrial hyperplasia. Normally, these tumours have a low grade endometrioid histology and tend to be biologically indolent. The molecular methods for precancerous diagnoses of the type I ECs that were developed recently, have expanded the range of detectable disease to a

Table 1 Classification of corpus uteri malignancies according to Blaustein's pathology(12) of the female genital tract and according to World Health Organisation (WHO) Classification of Tumours(13).

Blaustein	WHO
Epithelial Endometrial Carcinoma (EEC)	**Epithelial Endometrial Carcinoma (EEC)**
- Endometrioid adenocarcinoma (EAC)	- Endometrioid adenocarcinoma (EAC)
- EAC with adenosquamous differentiation	- EAC with adenosquamous differentiation
- Variants of EAC	- Variants of EAC
- Mucinous adenocarcinoma	- Mucinous adenocarcinoma
Non Endometrioid Endometrial carcinoma (NEEC)	**Non Endometrioid Endometrial carcinoma (NEEC)**
- Serous carcinoma (uterine papillary serous carcinoma)	- Serous adenocarcinoma
- Clear cell carcinoma	- Clear cell adenocarcinoma
- Adenosquamous carcinoma	
- Large cell carcinoma/undifferentiated carcinoma	- undifferentiated carcinoma
- Squamous cell carcinoma	- Squamous cell carcinoma
- Small cell carcinoma	- Small cell carcinoma
- Transitional cell carcinoma	- Transitional cell carcinoma
- Neuroendocrine differentiation	- Neuroendocrine differentiation
- Mixed cell adenocarcinoma	- Mixed cell adenocarcinoma
Sarcomas	**Sarcomas**
- Leiomyosarcoma	- Leiomyosarcoma epithelioid
	- Leiomyosarcoma Myxoid
- Endometrial stromal sarcoma high grade	- Undifferentiated Endometrial stromal sarcoma
- Endometrial stromal sarcoma low grade	- Endometrial stromal sarcoma, low grade
- Sarcoma other / not otherwise specified (NOS)	- Sarcoma other / not otherwise specified (NOS)
- Rhabomyosarcoma	- Rhabomyosarcoma
Mixed epithelial and mesenchymal tumours	**Mixed epithelial and mesenchymal tumours**
- Carcinosarcoma (Malignant Müllerian mixed tumour)	- Carcinosarcoma (Malignant Müllerian mixed tumour)
- Adenosarcoma	- Adenosarcoma
Type unclear / unspecified	**Type unclear / unspecified**
Other	**Other**

preclinical level, disclosing a much higher prevalence of early disease than previously suspected. The precancerous scenario for type I ECs begins with sporadic acquisition of rare PTEN mutation bearing glands. The genetic damage results in a progression to discrete foci of cytologically altered glands visible on routinely stained sections(20). Mutter(21) et al. developed a new definition for precancerous lesions: the endometrial intraepithelial neoplasia (EIN) (Tables 2a and 2b).

Table 2a Diagnostic classes from hyperplasia to cancer

Nomenclature	Topography	Functional category	Treatment
Benign endometrial hyperplasia (unopposed Oestrogen effect)	Diffuse	Oestrogen effect	Hormonal therapy
EIN[1]	Focal progressing to diffuse	Pre-cancer	Hormonal or surgical
Carcinoma	Focal progressing to diffuse	Cancer	Surgical Stage based

[1] EIN: Endometrial intraepithelial neoplasia

Table 2b Criteria for endometrial intraepithelial neoplasia (EIN) Criteria

EIN[1] criterion	Comments
Architecture	Area of glands > stroma (VPS [2] < 55%)
Cytology	Cytology differs between architecturally crowded focus and background
Size > 1mm	Maximum linear dimension exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria: Basalis, secretory, polyps, repair, etc.
Exclude cancer	Carcinoma if mazelike glands, solid areas or significant cribriforming

All criteria must be met for the diagnosis of EIN according to *Pathology and genetics of tumours of female genital organs* (WHO 2003);
[1] EIN: endometrial intraepithelial neoplasia; [2]VPS: volume percentage stroma.

Type II cancers are not oestrogen driven and arise in the presence of atrophic endometrium. Type II ECs are characterized by p53 mutations and have a worse prognosis compared to type I ECs. Examples of Type II cancers are serous adenocarcinoma, clear cell carcinoma, and squamous cell carcinomas (Table 1). Recently, the classification changed to endometrioid endometrial carcinoma (EEC) and non-endometrioid endometrial carcinoma (NEEC) (Table 1).

Endometrioid Endometrium Carcinoma (EEC)

EEC refers to a malignancy that arises from the endometrium of the uterus and, more specifically, from the epithelial cells that line the endometrium. Postmenopausal bleeding is an early presenting symptom of EEC and therefore most patients (75%) are diagnosed during the early stage of the disease. The endometrioid carcinomas are often preceded by a histologically evident precursor lesion. EEC and its precursor lesions are associated with excess estrogenic stimulation of the endometrium, resulting in proliferative glandular epithelial changes(12). The WHO 94 outline(12) for endometrial hyperplasia was recently replaced by the more reproducible EIN (endometrial intraepithelial neoplasia) schedule(22) (Tables 2a and 2b). EIN is diagnosed by the presence of cytological demarcation, glandular crowding (volume percentage stroma, VPS< 55%), minimum size of 1 mm, and careful exclusion of mimics(21) (Table2b).

Risk factors

Any factor that increases exposure to unopposed oestrogens, such as unopposed menopausal replacement treatment, obesity, and irregular menstrual cycles, e.g. polycystic ovary syndrome (PCOS), tends to increase the risk of EEC. Conversely, factors that decrease exposure to oestrogens or increase progesterone levels, such as oral contraceptives or smoking, tend to protect against EEC (Table 3)(23). The role of other factors, such as births, miscarriages, diabetes, and hypertension are more complicated to explain with models of carcinogenesis. The incidence rates for EEC were higher in more affluent countries and urban populations. Moreover, a substantial body of suggestive epidemiological evidence on the relation between diet and the increasing incidence of EEC has become available(24). In many Western countries, people's diets changed substantially during the second half of the 20th century. Generally, the consumption of meat, dairy products, vegetable oils, fruit juice, and alcoholic beverages increased, while the consumption of starchy staple foods such as bread, potatoes, rice, and maize flour decreased(25). Other aspects of lifestyle also changed, most notably a substantial reduction in physical activity and the alarming increase in the prevalence of obesity(26). Energy intake, energy expenditure, and BMI have been shown to be independent risk factors that influence the risk of cancer of the corpus uteri(24;27-29).

Staging and treatment

The majority of women (75%) with EEC are diagnosed in an early stage, they are postmenopausal and in 95% of cases abnormal vaginal blood loss is the first symptom. In 1988, the International Federation of Gynaecology and Obstetrics (FIGO) revised the staging system of endometrial cancer to mandate surgical dissection(30). In 2009 it was revised once more(31). Since we did the majority of analyses for this thesis prior to 2009, the stages of disease depicted refer to the FIGO staging of 1988 (Table 4).

Table 3 Risk factors for EEC.

Risk-increasing factors	Risk-decreasing factors
Increasing age	Grand multiparity
Long-term exposure to unopposed oestrogens	Smoking
Living in North America or Europe	Oral-contraceptive use
High concentrations of oestrogens postmenopausal	Physical activity
Metabolic syndrome (obesity, diabetes)	Diet of some phyto-oestrogen
Years of menstruation	
Nulliparity	
History of breast cancer	
Long-term use of tamoxifen	
Hereditary non-polyposis colorectal cancer syndrome	
Hormone-replacement therapy with less than 12 to 14 days of progestogens	
First-degree relative with endometrial cancer	

The cornerstone of treatment in early stage EEC is a total hysterectomy with bilateral salpingo-oophorectomy (TH-BSO)(32). Minimal invasive techniques like laparoscopy and robotic surgery are preferred(32-35). Since 2000, adjuvant therapy radiotherapy in stage I EEC is advised when two out of three risk factors are positive (> ½ myometrial invasion, ≥ 60 years of age, and/or grade III disease)(36;37). After 2007, adjuvant radiotherapy changed from external beam radiotherapy to vaginal brachytherapy(38). Although the main route of spread for endometrial cancer is through lymphatic dissemination, the role of lymphadenectomy for women with early stage endometrial tumours remains controversial(39-42). The Dutch guidelines do not recommend lymphadenectomy in low to intermediate risk EEC. The most important tumour-related prognostic factors in EC are stage of disease, myometrial invasion, histological grade, and lymphovascular space involvement (LVSI). Because only a small proportion of patients is diagnosed with advanced stages EC (stage III/IV), treatment modalities for these patients tend to evolve slowly and treatment is frequently individualised since limited evidence is available(43). The survival rate improved of patients with advanced endometrial cancer, in whom optimal surgical cytoreduction was achievable with adjuvant radiotherapy or adjuvant chemotherapy(44;45). In case of vaginal involvement the Dutch National Oncology Guidelines suggest to start with radiation therapy(46). The major contribution of external beam radiotherapy is the improvement of locoregional control. If primary cytoreduction is not possible then primary radiotherapy(47) is indicated, or systemic therapy with chemotherapy, or hormone therapy. Progesterone is the cornerstone of hormonal therapy(32;48;49). The advanced

Table 4 The FIGO staging and TNM classification of 1988 and 2009(31) (the changes in FIGO staging 2009 are in **bold**).

1988					2009			
FIGO Stages[1]		**TNM[1]**			**FIGO stages[1]**	**TNM[1]**		
		T	**N**	**M**		**T**	**N**	**M**
I	IA	T1a	No	Mo	**IA[2]**	T1a	No	Mo
	IB	T1b	No	Mo	**IB[3]**	T1b	No	Mo
	IC	T1c	No	Mo			No	Mo
II	IIA	T2a	No	Mo	**II[4]**	T2	No	Mo
	IIB	T2b	No	Mo			No	Mo
III	IIIA	T3a	No	Mo	**IIIA[5]**	T3a	No	Mo
	IIIB	T3b	No	Mo	IIIB	T3b	No	Mo
	IIIC	T1-3	N1	Mo	IIIC	T1-T3	N1	Mo
					IIIC1	T1-3	N1pelvic	Mo
					IIIC2	T 1-3	N1aortic	Mo
IV	IVA	T4	Any N	Mo	IVA	T4	Any N	Mo
	IVB	Any T	Any N	M1	IVB	Any T	Any N	M1

[1] Either G1, G2, or G3.
[2] FIGO 2009 IA < ½ invasion the myometrium (FIGO 1988 IA en IB)
[3] FIGO 2009 IB ≥ ½ invasion of the myometrium (FIGO 1988 IC)
[4] Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
[5] Positive cytology has to be reported separately without changing the stage (in FIGO 1988 pos cytology upstaged T1-2 to IIIA). *In the presence of adnexal involvement, positive cytology upstages Stage IIIA to IIIC.*

stages are diagnosed more frequently in the elderly (≥75 years) with co- morbidity and geriatric problems. Geriatric oncology is a fast developing specialism and research is done to develop screening instruments to detect the fit elderly patient, who will tolerate staging procedures and adjuvant therapy well. The more frail elderly, who are at greater risk of complications and adverse side-effects from the surgical therapy, radiotherapy, and chemotherapy therapy, have to be offered alternative option(50).

Non-endometrioid endometrial carcinoma (NEEC)

These tumours are not oestrogen driven, have a higher grade, and generally their prognoses are poor(51). As shown in Table 1 examples of NEEC are serous carcinoma (uterine papillary serous carcinoma), clear cell carcinoma, adenosquamous carcinoma,

large cell carcinoma/undifferentiated carcinoma, squamous cell carcinoma, small cell carcinoma, transitional cell carcinoma, neuroendocrine differentiation, mixed cell adenocarcinoma. In Chapter 2, Section 2, we describe the incidence and survival trends of NEECs in the Netherlands from 1989 to 2008. The most frequently diagnosed rare endometrial carcinomas are serous carcinoma and clear cell carcinoma(52).

Serous carcinoma also known as uterine papillary serous carcinoma (UPSC)

In 1982, Hendrickson et al.(14) described uterine papillary serous carcinoma as a highly malignant subtype of endometrial carcinoma characterised by a complex papillary architecture with tufted stratification of the epithelial lining, a high nuclear to cytoplasmic ratio, notable nuclear pleomorphism, macronuclei, and a high rate of mitosis. This carcinoma almost always stains positive for p53 and tends not to express oestrogen and progesterone receptors(12). Endometrial intraepithelial carcinoma (EIC) is considered a precursor lesion of serous carcinoma. Histologically, uterine papillary serous carcinoma closely resembles ovarian papillary serous carcinoma, and psammoma bodies might be present. Patients with serous carcinoma are a median of five years older than those with endometrioid cancers and their prognoses are poor. Serum cancer antigen 125 (CA 125) concentrations are frequently raised in patients with uterine papillary serous carcinoma. The metastatic spread of uterine papillary serous carcinoma is commonly intra-abdominal, in a manner resembling ovarian cancer(53;54). Like endometrioid cancer, it usually presents with vaginal bleeding. The name papillary serous carcinoma should not be confused with the term papillary carcinoma, which describes the architectural pattern seen in various cell types, and generally applies to villoglandular tumours, a low-grade subset of endometrioid endometrial cancers(55). Patients with serous carcinoma have a poor five-year overall survival; in the literature five-year survival rates between 20-50% are mentioned(56-59). Most uterine papillary serous carcinomas have spread outside the uterus by the time of presentation and even in cases that are apparently confined to the uterus, the majority of patients develop recurrent disease.

Clear Cell Carcinoma (CCC)

In 1976(60), an extensive clinicopathological description of CCC was published with the following characteristics: clear and hobnail-shaped cells, a high incidence of pelvic endometriosis in admixtures with endometrioid carcinoma, tumours arising from the epithelium of an endometrial cyst. If immunohistochemistry information is added, CCC is often ER and PR positive. Patients with clear cell carcinoma are a median of five years older than those with endometrioid cancers and their prognoses are poor. In studies in which surgically staging was optimal, improved survival rates were found for patients with stage I disease compared to clinical stage I disease(7). Clear-cell carcinoma and uterine papillary serous carcinoma constituted only about 10% of endometrial carcinomas but were associated with about 50% of relapses(57;61;62).

Mesenchymal tumours/sarcomas

Malignant mesenchymal tumours or sarcomas of the uterus are uncommon and constitute a mere 3% of uterine malignancies. According to the 2003 World Health Organization (WHO) classification(13), they consist of two main groups: mesenchymal tumours and mixed epithelial and mesenchymal tumours. The pure mesenchymal tumours can be further classified into endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), including the epithelioid and myxoid variants, and undifferentiated endometrial/uterine sarcoma (UUS) according to the cell of origin. Mixed tumours include carcinosarcoma and adenosarcoma and are composed of a mixture of epithelial and mesenchymal components. Carcinosarcoma (mixed mesodermal tumour or malignant mixed Müllerian tumour MMMT) are regarded as a subset of endometrial carcinoma, and as such should be excluded from studies of uterine sarcoma. Nevertheless, carcinosarcoma is still included in most retrospective studies of uterine sarcoma, as well as in the 2003 WHO classification.

Leiomyosarcomas

Leiomyosarcomas (LMSs) represent about 2% of uterine malignancies and 50% of the sarcomas. Median age is 50-55 years. The main symptoms are abnormal vaginal bleeding, lower abdominal pain, or a pelvic or abdominal mass. LMS is seldom associated with a history of pelvic radiation. The average diameter is 6-9 cm. Tumour cell necroses are typically prominent, invasion into the myometrium is common and 10-22% of the LMSs are identified with vascular invasion. The usual features of malignancy are generally present: cytological atypia, tumour cell necrosis and a high mitotic index. LMS is a highly aggressive tumour with a poor rate of survival. The incidence of lymph node involvement in lower stage LMS is low. Relapses are both locoregional and haematogenous. The prognosis of LMS depends on its stage. For stage I tumours some investigators found that a size of 5 cm or less is associated with improved survival. Treatment is hysterectomy with BSO. Prognoses are poor with five-year survival rates of 40%.

Endometrial stromal sarcoma

Endometrial stromal tumours are uncommon mesenchymal neoplasms of the uterus. They are the second most common pure mesenchymal tumour after leiomyosarcomas(13) Histologically and immunophenotypically they resemble normal endometrial stroma. Low grade ESS is a clinically indolent malignancy with minimal cytologic atypia and proliferative activity. The highly aggressive malignancy that shows substantial cytologic atypia and high mitotic activity was previously categorised as a high grade ESS, but is now referred to as undifferentiated stromal sarcomas (USS)(16). Median age is 52 years and 67% of the ESS is confined to the uterus, surgically stage I. Five and ten-year survival rates for stage I are 98% and 59%, respectively(63;64).

Endometrial carcinosarcoma/uterine carcinosarcoma; metaplastic subtype of endometrial cancer

Carcinosarcomas of the uterus, previously known as malignant mixed mesodermal tumours or malignant mixed Müllerian tumours (MMMT)(65), are highly aggressive. They account for 3.7% of the corpus uteri malignancies. The collision theory was replaced by the recent insight that carcinosarcomas have a monoclonal origin. The historical literature usually reported on studies of uterine sarcomas by lumping together carcinosarcomas (CS), leiomyosarcomas (LMS), and endometrial stromal sarcomas (ESS)(66), but recent studies found that the aetiology of CS is distinct from that of LMS(17;67). Currently, investigators propose to rename CS as metaplastic carcinoma since it may arise from a common stem cell that produces epithelial tumours with a bi-phasic development which allows for the mixed histological appearances (17;67;68). Nowadays, this conversion theory is generally accepted. Recent textbooks, therefore, classify carcinosarcomas as a subtype of endometrial cancer(12). The epithelial component is the driving force. Carcinosarcoma has a high tendency to early extrauterine spread and as a consequence, advanced disease is usually present at the time of diagnosis. The prognoses are poor, five-year survival rates have been reported between 30% and 45.8% in early stage and 0-10% in advanced stage CS (69).

Patient characteristics

Age and the elderly patient

The number of elderly patients with cancer is increasing and 30% of all newly diagnosed cancer patients are 75 years and older. Consequently, there is a need to unravel issues in the field of management of elderly patients with cancer(70). The prognosis of cancer decreases with increasing age due to a more unfavourable histology, a more unfavourable stage distribution, referral bias, diminishing tendency by physicians to perform diagnostic procedures in elderly patients, and a tendency to adhere less to treatment guidelines(71) where it concerned the elderly, because of the pessimistic attitudes of care providers. Furthermore, elderly patients are underrepresented in clinical trials. Population-based studies are necessary to bridge the gap between clinical trials and usual care. For cancer of the corpus uteri we face the increasing incidence of EEC due to aging of the population. In addition, NEEC and sarcomas with unfavourable prognoses occur more often in elderly women. In this thesis we present incidence, treatment, and survival according to age. Concomitant diseases like diabetes, cardiovascular disease, and pulmonary disease influence life expectancy. It would not be realistic to approach life expectancy solely from an oncological point of view, with a clinical reality based only on stage and histological type. In elderly patients the number of concomitant diseases or co-morbidity increases(72). It is important to analyse the oncologic data against the background of co-morbidity.

Fortunately, the Eindhoven Cancer Registry (ECR), one of the world best known sources of population-based data on co-morbidity in cancer patients, offers us the data to address some of the issues relevant to elderly patients as mentioned here.

Co-morbidity

The prognosis of cancer decreases with increasing age, although this difference is less if we take into account deaths due to other causes. A more precise prognostic index would include histologic type, FIGO stage, and concomitant diseases, also called co-morbidity, including diabetes mellitus, cardiovascular diseases, and pulmonary diseases. Co-morbidity was defined as life-shortening diseases that were present at the time of cancer was diagnosed. One of the most commonly used indexes was developed by Charlson et al.(73) This index has been comprehensively analysed and adapted. Since Charlson's publication in 1987 many scoring systems were developed and validated to predict mortality in patients with a combination of diseases(50;74-77). In the ECR an adapted list, based on the Charlson Index, is used for the registration of concomitant diseases or co-morbidity (Table 5). Several studies showed an independent negative prognostic effect of co-morbidity on survival of cancer. The increased risk of death is associated with the co-morbid condition itself, but also to contra-indications for anti-cancer treatment and more treatment-related complications, because of the co-morbidity.

The prevalence of co-morbidity usually increases with age. About 60% of all new cancer patients older than 65 suffered from at least one other serious disease. Janssen-Heijnen et al. found that most frequent concomitant diseases are previous cancers, heart disease, hypertension, COPD, and diabetes mellitus, with prevalence rates up to 20%, 23%, 26%, 17%, and 16%, respectively(78). The prevalence of hypertension was highest among women with cancer of the corpus uteri or kidney. High prevalence rates of diabetes in older patients were observed for cancer of the corpus uteri (79) (Table 6).
In this thesis we analysed treatment and survival in stage I EEC in relation to co-morbidity.

Diabetes mellitus and endometrioid endometrial carcinoma

A growing body of evidence indicates that diabetes mellitus (DM) is associated with an increased risk of developing cancer. The mechanisms are yet to be elucidated, but insulin resistance with secondary hyperinsulinemia is the most supported hypothesis since it may have a mitogenic effect by activating insulin-like growth factor-1 receptors(80-83). Meta-analyses have recognized that DM increases the risks of endometrium cancer (84). Type 2 DM is characterized by insulin resistance and secondary hyperinsulinemia. Subjects with type 2 DM are more often obese and less active, which probably also contributes to hyperinsulinemia. Hyperinsulinemia and hyperglycaemia have also been reported to promote tumour cell proliferation and metastases in type 2 DM. This hypothesis is supported by evidence that treatment with Metformin (widely given to patients with type

Table 5 Classification of co-morbidity according to an adapted list based on Charlson

Previous malignancies (except basal cell skin carcinoma and cervix carcinoma in situ)
Chronic obstructive pulmonary diseases
-1 Cardiovascular diseases -2 Myocardial infarction -3 Heart failure -4 Angina pectoris -5 Intermittent claudication -6 Abdominal aneurysm -7 Cardiomyopathy -8 Valve prosthesis (aorta or mitral)
Cerebrovascular diseases -9 Cerebrovascular accident -10 Hemiplegia
Hypertension
Digestive tract diseases -11 Ulcerative disease (only registered since 1997) -12 Patients who underwent major surgery for ulcerative disease (Billroth I or II) -13 Chronic inflammatory diseases (Crohn's disease, ulcerative colitis except polyposis coli)
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other -14 Urinary tract diseases -15 Connective tissue diseases -16 Dementia -17 Chronic infections

2 DM, works by targeting the enzyme AMP activated protein kinase, which induces muscles to take up glucose from the blood), is associated with a lower incidence of cancer in diabetic patients than therapy with insulin(85;86). The effect of DM on the risk of cancer may be small, given the high incidence of both DM and EEC, even a modest association between DM and cancer means a considerable effect on public health. Furthermore, the number of newly diagnosed cancer patients with DM is expected to double from 5 500 in 2000 to 10 400 in 2015(87). The decline of survival from 86% to 74% in patients with DM in early stage EEC is further analysed in a cohort study of a group of 388 EEC patients, with 193 DM patients to answer questions on relation of DM according to stage distribution, grade, disease-specific survival, and glycaemic control (Chapter 3.2. of this thesis).

Table 6 Prevalence of severe and acknowledged co-morbidity in corpus uteri malignancy according to age in the southern part of the Netherlands from 2000 to 2009 (N=2227).

	50-64	65-79	80+
Co-morbidity total (%)	43	68	80
Previous malignancy (%)	9	14	20
Cardiovascular disease (%)	9	22	38
COPD (%)	4	6	7
Hypertension (%)	24	41	42
Diabetes (%)	12	21	25

Eindhoven Cancer Registry (ECR), 2011

Cancer registries

For the studies in this thesis data from the Eindhoven Cancer Registry, the Netherlands Cancer Registry, and several international population-based databases were used.

The Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) started in 1955 as part of a nation-wide cancer registration programme in the Netherlands. Data on all new cancer patients were collected directly from pathology reports and medical records, sometimes through hospital discharge registries. The registry was started in three hospitals in Eindhoven and gradually expanded to include the south-eastern part of the province of North Brabant, the northern part of the province of Limburg (since 1970) and the middle and south-western part of North Brabant since 1986 (except for a small, most western part) (Figure 3). The region is characterised by good access to medical care without financial obstacles. The distance to a hospital for all inhabitants was always less than 30 kilometres. The population in the area is aging markedly due to longer life expectancy and a decreasing number of births since 1970. This results in an increased proportion of elderly people. The area of the population-based ECR now covers 2.4 million inhabitants, ten general hospitals at sixteen locations, six regional pathology laboratories, two large radiotherapy institutes, and one neurosurgical centre.

The Netherlands Cancer Registry

The regional registries, other than the ECR, had discontinued their activities, until a new nation-wide programme was established in 1984 following the ECR's example in terms of data collection. Since 1989 the whole Dutch population is covered by nine regional cancer

registries, which combined to form the Netherlands Cancer Registry (NCR) governed by the Association of Comprehensive Cancer Centres. By 2011, two remained, the Comprehensive Cancer Centre the Netherlands (IKNL) and Comprehensive Cancer South (IKZ), the latter of which hosts ECR. The Dutch cancer registries receive notifications of all newly diagnosed malignancies via the automated national pathology archive (PALGA). Additional sources are the national registry of hospital discharge, haematology departments, laboratories, and radiotherapy institutes. Completeness is estimated to be at least 95%. Trained registration clerks actively collect data from hospital records on diagnosis, topography, histology, stage, and information about primary treatment (delivered within six months of diagnosis). The medical record is generally regarded as the most complete source of information on the patient's past and current health status. Information on the vital status of the patients was initially obtained from the municipal registries and from 1995 onwards from the nation-wide population registries network. These registries provide virtually complete coverage of all deceased citizens of the Netherlands.

Quality of life studies and the PROFILES registry

The actual benefit from progress against uterine malignancies needs to be analysed in relation to the long-term sequelae of cancer management and the health-related quality of life (HRQoL) of cancer survivors. The number of long-term EEC survivors will increase substantially, approximately 3-5% per year. The Quality of Life Group of the European Organisation for Research and Treatment of Cancer (EORTC-QoL)(88) has developed a core self-report questionnaire, the QLQ-C30(88;89), for assessing the QoL of patients with cancer. The QLQ-C30 was originally designed for use in cancer clinical trials and other observational studies during the period of active treatment and shortly thereafter. Increasingly, however, the QLQ- C30 is being used in longer term cancer survivorship studies(90;91). Sexuality items are not included in the EORTC QLQ-C30, but are incorporated in the EORTC questionnaire modules for breast, prostate, head and neck, ovarian, cervix, and colorectal cancer. Dutch men and women reported high levels of overall QoL compared to previously published Scandinavian and German normative data. The endometrial cancer module, QLQ-EN24, was developed in accordance with the EORTC guidelines for module development(92; 93). It should be noted that QLQ-EN24 does not measure sexual functioning comprehensively but it includes important areas and in this study more than two thirds (74%) of the patients were not sexually active. An initiative to monitor long-term physical and psychosocial impact of cancer was taken by the University of Tilburg together with IKZ by starting PROFILES (which stands for patient-reported outcomes following initial treatment and long term evaluation of survivorship). PROFILES contains a large web-based component and is linked directly to clinical data from the population-based Eindhoven Cancer Registry(94;95). The main objectives of PROFILES are to generate data relevant to psychosocial risk and outcome assessment to identify patients

at high risk of poor health outcomes. To analyse mediating mechanisms to better understand the biological and behavioural factors associated with cancer treatment outcomes. To evaluate physical and psychosocial care (needs) of cancer survivors. In this thesis we used the data from the PROFILES Registry to study the effect of BMI on the quality of life of endometrial cancer survivors. It was considered important to compare data of cancer survivors with data of a normative population. The latter was obtained from CentERpanel, an online household panel representative of the Dutch population with annual data collection(96).

Outline thesis

In Chapter 1 the aim of the study and an overview of the literature are presented. Chapter 2 describes the trends in corpus uteri malignancies in population-based studies using the data from the Dutch National Cancer Registry from 1989 to 2009. Section 1 emphasises the most common type of endometrial cancer, endometrioid endometrial carcinoma (EEC), the incidence of which is increasing. In section 2 a description of the effects on survival of the implementation of evidence-based treatment like the results of PORTEC-1(36) and PORTEC-2(97) is presented. In Section 3 the trends in incidence and survival of uncommon corpus uteri malignancies, non-endometrioid endometrial carcinoma (NEEC) and sarcomas, are described followed in. In chapter 3 an analysis is presented on patient characteristics, such as age and co-morbidity, on treatment and survival in women with early stage EEC, based on data from the Eindhoven Cancer Registry from 1995 to 2008. In addition, an evaluation was conducted of the adherence to national guidelines and the role of co-morbidity was investigated. In Section 3.2 a retrospective cohort study on the influence of DM on cancer stage at diagnosis, cancer recurrence, and survival of endometrial cancer (EC) patients will be presented. Moreover, we analysed the influence of the treatment of EEC on glycaemic control, treatment, and complications of DM with data from the ECR in the period from 2000 to 2008. In Chapter 4 the influence of co-morbidity, such as higher BMI, on the quality of live in EC survivors will be presented. This analysis was conducted with data from the PROFILES Registry from 1999 to 2007. Findings of this thesis are discussed in Chapter 5, beginning with a discussion in Section 1 on the question whether we might be able to improve survival and decrease mortality in unfavourable corpus uteri malignancies. In Section 2 the main findings on tumour and patient characteristics are summarised and I conclude by discussing what the impact might be of the trends found on future policy with regards to diagnosis and treatment of corpus uteri malignancies.

Reference List

(1) Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de VE. Progress against cancer in the Netherlands since the late 1980s: An epidemiological evaluation. Int J Cancer 2011 Jul 25.

(2) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010 Dec 15;127(12):2893-917.

(3) Karim-Kos HE, de VE, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer 2008 Jul;44(10):1345-89.

(4) Duong LM, Wilson RJ, Ajani UA, Singh SD, Eheman CR. Trends in endometrial cancer incidence rates in the United States, 1999-2006. J Womens Health (Larchmt) 2011 Aug;20(8):1157-63.

(5) Evans T, Sany O, Pearmain P, Ganesan R, Blann A, Sundar S. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. Br J Cancer 2011 Apr 26;104(9):1505-10.

(6) Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. Eur J Cancer 2011 Sep;47(14):2202-10.

(7) Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006 Nov;95 Suppl 1:S105-S143.

(8) Trovik J, Mauland KK, Werner HM, Wik E, Helland H, Salvesen HB. Improved survival related to changes in endometrial cancer treatment, a 30-year population based perspective. Gynecol Oncol 2012 Feb 1.

(9) Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. J Natl Cancer Inst 2010 Oct 20;102(20):1584-98.

(10) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011 Mar;61(2):69-90.

(11) Harteloh P, de BK, Kardaun J. The reliability of cause-of-death coding in The Netherlands. Eur J Epidemiol 2010 Aug;25(8):531-8.

(12) Robert J.Kurman. Blaustein's Pathology of the Female Genital Tract. sixth edition 2011.

(13) Tavassoli F.A., Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. WHO 2003 Jan 1.

(14) Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. Am J Surg Pathol 1982 Mar;6(2):93-108.

(15) Abeln EC, Smit VT, Wessels JW, de Leeuw WJ, Cornelisse CJ, Fleuren GJ. Molecular genetic evidence for the conversion hypothesis of the origin of malignant mixed mullerian tumours. J Pathol 1997 Dec;183(4):424-31.

(16) Amant F, Vergote I, Moerman P. The classification of a uterine sarcoma as 'high-grade endometrial stromal sarcoma' should be abandoned. Gynecol Oncol 2004 Nov;95(2):412-3.

(17) Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. Lancet Oncol 2009 Dec;10(12):1188-98.

(18) Clement PB, Young RH. Endometrioid carcinoma of the uterine corpus: a review of its pathology with emphasis on recent advances and problematic aspects. Adv Anat Pathol 2002 May;9(3):145-84.

(19) Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983 Feb;15(1):10-7.

(20) Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Eng C. Changes in endometrial PTEN expression throughout the human menstrual cycle. J Clin Endocrinol Metab 2000 Jun;85(6):2334-8.

(21) Mutter GL. Diagnosis of premalignant endometrial disease. J Clin Pathol 2002 May;55(5):326-31.

(22) Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of Endometrial Precancers. Obstet Gynecol 2012 Nov;120(5):1160-75.

(23) Amant F, Moerman P, Neven P, Timmerman D, Van LE, Vergote I. Endometrial cancer. Lancet 2005 Aug 6;366(9484):491-505.

(24) Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer 2010 Sep;46(14):2581-92.

(25) Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW, et al. Incident cancer burden attributable to excess body mass index in 30 European countries. Int J Cancer 2010 Feb 1;126(3):692-702.
(26) Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010 Jul 15;127(2):442-51.
(27) Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. Curr Oncol Rep 2011 Feb;13(1):71-6.
(28) Boniol M, Autier P. Prevalence of main cancer lifestyle risk factors in Europe in 2000. Eur J Cancer 2010 Sep;46(14):2534-44.
(29) van der Wilk EA, Jansen J. Lifestyle-related risks: are trends in Europe converging? Public Health 2005 Jan;119(1):55-66.
(30) Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet 2008 May;101(2):205-10.
(31) Lewin SN. Revised FIGO staging system for endometrial cancer. Clin Obstet Gynecol 2011 Jun;54(2):215-8.
(32) Wright JD, Barrena Medel NI, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management of endometrial cancer. Lancet 2012 Apr 7;379(9823):1352-60.
(33) Mourits MJ, Bijen CB, Arts HJ, ter Brugge HG, van der Sijde R, Paulsen L, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol 2010 Aug;11(8):763-71.
(34) Fader AN, Seamon LG, Escobar PF, Frasure HE, Havrilesky LA, Zanotti KM, et al. Minimally invasive surgery versus laparotomy in women with high grade endometrial cancer: a multi-site study performed at high volume cancer centers. Gynecol Oncol 2012 Aug;126(2):180-5.
(35) Subramaniam A, Kim KH, Bryant SA, Zhang B, Sikes C, Kimball KJ, et al. A cohort study evaluating robotic versus laparotomy surgical outcomes of obese women with endometrial carcinoma. Gynecol Oncol 2011 Sep;122(3):604-7.
(36) Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000 Apr 22;355(9213):1404-11.
(37) Dutch National Oncology Guidelines. www oncoline nl 2004.
(38) Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev 2012;3:CD003916.
(39) Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009 Jan 10;373(9658):125-36.
(40) Benedetti PP, Basile S, Maneschi F, Alberto LA, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008 Dec 3;100(23):1707-16.
(41) Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010 Apr 3;375(9721):1165-72.
(42) Mariani A, El-Nashar SA, Dowdy SC. Lymphadenectomy in endometrial cancer: which is the right question? Int J Gynecol Cancer 2010 Oct;20(11 Suppl 2):S52-S54.
(43) van Wijk FH, van der Burg ME, Burger CW, Vergote I, van Doorn HC. Management of surgical stage III and IV endometrioid endometrial carcinoma: an overview. Int J Gynecol Cancer 2009 Apr;19(3):431-46.
(44) van Wijk FH, Huikeshoven FJ, Abdulkadir L, Ewing PC, Burger CW. Stage III and IV endometrial cancer: a 20-year review of patients. Int J Gynecol Cancer 2006 Jul;16(4):1648-55.
(45) Humber CE, Tierney JF, Symonds RP, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol 2007 Mar;18(3):409-20.
(46) Dutch National Oncology Guidelines. www oncoline nl 2004.
(47) Wegner RE, Beriwal S, Heron DE, Richard SD, Kelly JL, Edwards RP, et al. Definitive radiation therapy for endometrial cancer in medically inoperable elderly patients. Brachytherapy 2010 Jul;9(3):260-5.
(48) Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev 2010;(12):CD007926.

(49) Cade TJ, Quinn MA, Rome RM, Neesham D. Progestogen treatment options for early endometrial cancer. BJOG 2010 Jun;117(7):879-84.
(50) Maas HA, Janssen-Heijnen ML, Olde Rikkert MG, Machteld Wymenga AN. Comprehensive geriatric assessment and its clinical impact in oncology. Eur J Cancer 2007 Oct;43(15):2161-9.
(51) Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006 Mar 13;94(5):642-6.
(52) Acharya S, Hensley ML, Montag AC, Fleming GF. Rare uterine cancers. Lancet Oncol 2005 Dec;6(12):961-71.
(53) Goff BA, Kato D, Schmidt RA, Ek M, Ferry JA, Muntz HG, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol 1994 Sep;54(3):264-8.
(54) Kato DT, Ferry JA, Goodman A, Sullinger J, Scully RE, Goff BA, et al. Uterine papillary serous carcinoma (UPSC): a clinicopathologic study of 30 cases. Gynecol Oncol 1995 Dec;59(3):384-9.
(55) Hendrickson MR, Longacre TA, Kempson RL. Uterine papillary serous carcinoma revisited. Gynecol Oncol 1994 Sep;54(3):261-3.
(56) Felix AS, Stone RA, Bowser R, Chivukula M, Edwards RP, Weissfeld JL, et al. Comparison of survival outcomes between patients with malignant mixed mullerian tumors and high-grade endometrioid, clear cell, and papillary serous endometrial cancers. Int J Gynecol Cancer 2011 Jul;21(5):877-84.
(57) Boruta DM, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009 Oct;115(1):142-53.
(58) Havrilesky LJ, Secord AA, Bae-Jump V, Ayeni T, Calingaert B, Clarke-Pearson DL, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol 2007 Jun;105(3):677-82.
(59) Martinez AA, Weiner S, Podratz K, Armin AR, Stromberg JS, Stanhope R, et al. Improved outcome at 10 years for serous-papillary/clear cell or high-risk endometrial cancer patients treated by adjuvant high-dose whole abdomino-pelvic irradiation. Gynecol Oncol 2003 Sep;90(3):537-46.
(60) Kurman RJ, Scully RE. Clear cell carcinoma of the endometrium: an analysis of 21 cases. Cancer 1976 Feb;37(2):872-82.
(61) Ueda SM, Kapp DS, Cheung MK, Shin JY, Osann K, Husain A, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008 Feb;198(2):218-6.
(62) Trope C, Kristensen GB, Abeler VM. Clear-cell and papillary serous cancer: treatment options. Best Pract Res Clin Obstet Gynaecol 2001 Jun;15(3):433-46.
(63) Chang KL, Crabtree GS, Lim-Tan SK, Kempson RL, Hendrickson MR. Primary uterine endometrial stromal neoplasms. A clinicopathologic study of 117 cases. Am J Surg Pathol 1990 May;14(5):415-38.
(64) Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer 2008 Oct 21;99(8):1210-5.
(65) Bitterman P, Chun B, Kurman RJ. The significance of epithelial differentiation in mixed mesodermal tumors of the uterus. A clinicopathologic and immunohistochemical study. Am J Surg Pathol 1990 Apr;14(4):317-28.
(66) Reed NS, Mangioni C, Malmstrom H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008 Apr;44(6):808-18.
(67) McCluggage WG. Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas? J Clin Pathol 2002 May;55(5):321-5.
(68) D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010 Jan;116(1):131-9.
(69) Amant F, Cadron I, Fuso L, Berteloot P, de JE, Jacomen G, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. Gynecol Oncol 2005 Aug;98(2):274-80.
(70) Cancer in the Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8 2012.
(71) Hoon SD, Kang S, Lim MC, Lee TS, Park JY, Kim TJ, et al. Management of the elderly patient with gynecologic cancer: report of the 2011 workshop in geriatric gynecologic oncology. Int J Gynecol Cancer 2012 Jan;22(1):161-9.

(72) Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005 Sep;55(3):231-40.
(73) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83.
(74) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992 Jun;45(6):613-9.
(75) Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. J Clin Epidemiol 1999 Feb;52(2):137-42.
(76) Yancik R. Epidemiology of cancer in the elderly. Current status and projections for the future. Rays 1997 Jan;22(1 Suppl):3-9.
(77) Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL, Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 2004 May 26;291(20):2441-7.
(78) Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005 Sep;55(3):231-40.
(79) Wymenga AM, Coebergh JW, Maas HA, chouten HC . Kanker bij ouderen/ Cancer in the elderly. de Tijdstroom 2011.
(80) Noto H, Osame K, Sasazuki T, Noda M. Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. J Diabetes Complications 2010 Sep;24(5):345-53.
(81) Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 2008 May 6;98(9):1582-5.
(82) Saltzman BS, Doherty JA, Hill DA, Beresford SA, Voigt LF, Chen C, et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. Am J Epidemiol 2008 Mar 1;167(5):607-14.
(83) Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia 2012 Jun;55(6):1619-32.
(84) Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007 Jul;50(7):1365-74.
(85) Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005 Jun 4;330(7503):1304-5.
(86) Monami M, Colombi C, Balzi D, Dicembrini I, Giannini S, Melani C, et al. Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2011 Jan;34(1):129-31.
(87) Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, Hamberg-van Reenen HH, Verkleij H, Heus S, et al. Diabetes till 2025; prevention and care in connection.(Diabetes tot 2025: prevetie en zorg in samenhang). RIVM-rapport 260322004 2009.
(88) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.
(89) Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001 Jul;37(11):1331-4.
(90) Hjermstad MJ, Fayers PM, Bjordal K, Kaasa S. Using reference data on quality of life--the importance of adjusting for age and gender, exemplified by the EORTC QLQ-C30 (+3). Eur J Cancer 1998 Aug;34(9):1381-9.
(91) Schwarz R, Hinz A. Reference data for the quality of life questionnaire EORTC QLQ-C30 in the general German population. Eur J Cancer 2001 Jul;37(11):1345-51.
(92) Sprangers M, Cull A, Groenvold M. Guidelines for developing questionnaire modules. EORTC Publications, Brussels 1997.
(93) Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 2011 Jan;47(2):183-90.
(94) van de Poll-Franse LV, Horevoorts N, van EM, Denollet J, Roukema JA, Aaronson NK, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011 Sep;47(14):2188-94.

(95) Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES). www profilesregistry nl 2012.
(96) van de Poll-Franse LV, Mols F, Gundy CM, Creutzberg CL, Nout RA, Verdonck-de Leeuw IM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. Eur J Cancer 2011 Mar;47(5):667-75.
(97) Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010 Mar 6;375(9717):816-23.

2

Trends

2.1. **Increased incidence and improved survival in Endometrioid Endometrial Cancer diagnosed since 1989 in The Netherlands: a population based study**

2.2. **Reduced adjuvant radiotherapy based increasingly on evidence-based treatment of patients with endometrioid endometrial carcinoma resulting in similar survival rates in the Netherlands between 1994 and 2009**

2.3. **Incidence and survival trends of uncommon corpus uteri malignancies in The Netherlands, 1989-2008**

2.1

Increased incidence and improved survival in Endometrioid Endometrial Cancer diagnosed since 1989 in The Netherlands: a population based study

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Eur J Obstet Gynecol Reprod Biol 2013; 166(2):209-214.

Abstract

Objectives

Measuring progress against endometrioid endometrial carcinoma (EEC) in The Netherlands by analysing trends in incidence, survival and mortality simultaneously.

Study design

Descriptive study of incidence, survival and mortality rates of women with EEC in The Netherlands. Rates were age-standardised to the European standard population. Population based data were extracted from the nationwide Dutch Cancer Registry (NCR) between 1989 and 2009. Mortality data since 1989 came from Statistics Netherlands. European age standardised incidence rates were calculated according to age, histology and stage. Five year relative survival estimates were calculated in four periods. Optimal progress against cancer is defined as decreasing incidence and/or improving survival accompanied by declining mortality.

Results

80% of the 32,332 patients newly diagnosed with a corpus uteri malignancy had an EEC. Incidence of EEC rose significantly from 11/100,000 to 15/100,000, being most pronounced in women with FIGO stage IB and in the group with grade 1&2 tumours ($P < 0.05$). Coinciding with the increased incidence, five year relative survival increased, especially for patients aged 60-74 years, in women with FIGO stage I, and in histology group grade 1&2, being 87%, 94% and 93%, respectively, during 2005-09.

Conclusion

The incidence of EEC (being 80% of corpus uteri cancer) increased markedly between 1989 and 2009, especially in women of 60-74 years. Five-year survival for patients with EEC increased from 83 to 85%. Progress against EEC has been less than was assumed previously, because of the increasing incidence. And although survival improved mortality proportionally decreased only slightly.

Introduction

Worldwide, malignancy of the corpus uteri is the fifth most common cancer in women, accounting for almost 5% of all malignancies in women, and being the 10th leading cause of cancer deaths in the world[1]. In 2008, on a worldwide basis, there were about 287,000 new cases and 74,000 deaths. Approximately 2.6% of all women will develop a corpus uteri malignancy in their lifetime[2].

The most common subtype of corpus uteri malignancy is endometrioid endometrial carcinoma (EEC), which is related to increased exposure to estrogens, either endogenous or exogenous[3]. Estrogen exposure influences the progression from proliferative endometrium through hyperplasia and hyperplasia with atypia to EEC. The most important risk factor for the development of EEC is unopposed estrogen and as a result from the production of estrone by adipose tissue, obesity is also an important risk factor for EEC[4;5]. Survival for patients with EEC improved largely by a shift towards a more favourable stage distribution. The non-endometrioid types (NEEC), which behave more aggressively and have a poorer prognosis than EEC[6;7], showed a decreased incidence in The Netherlands. Recently we reported on this decreased incidence and survival for Dutch patients with NEEC and sarcomas diagnosed during 1989-2008[8], because shifts in the distribution between subtypes such as sereus adenocarcinoma of the endometrium. Mortality in corpus uteri cancer is positively influenced by improved survival in EEC and by the decrease of subtypes, with poorer prognosis.

Progress in the prevention and treatment of cancer in The Netherlands since the late 1980s was recently described for 23 major cancer types[9]. The framework used in this epidemiological evaluation combined incidence, survival and mortality to achieve a more objective assessment of progression against cancer. Increased survival and a decline in mortality indicate that some progression against corpus uteri cancer has been achieved between 1989 and 2008 in The Netherlands.

In this study we examined the progress against corpus uteri malignancy in more detail. We analysed incidence, survival and mortality trends of corpus uteri malignancies in The Netherlands according to stage and grade during the period of 1989-2009. We emphasized the largest group of women, those with EEC, because of the importance of this patient group in the determination of future health policy and the allocation of health care resources.

Materials and Methods

This study is part of the Dutch Cancer Society project on measuring progress against cancer in The Netherlands which started in the late 1980s[9]. Optimal progress against cancer is defined as decreasing incidence and/or improving survival accompanied by

declining mortality. Deterioration is defined as increasing incidence and/or deteriorating survival accompanied by increasing mortality rates.

Data collection

For the present study population based data were extracted from the nationwide Dutch Cancer Registry (NCR), which was started in 1989. The NCR is based on the notification of newly diagnosed malignancies by the automated nationwide pathological archive (PALGA). Information on patient characteristics like gender, date of birth, and tumour characteristics such as date of diagnosis, sub site (ICD-54)[10], histology, stage (Tumour Lymph Node Metastasis (TNM) classification) grade[11], and primary treatment, were obtained routinely from the medical records. Completeness of the NCR data is estimated to be at least 95%[12]. All patients with invasive corpus uteri cancer (International Classification of Diseases for Oncology: C54.0 - C54.9)[10] diagnosed in The Netherlands during the period of 1989–2009 were included (*n*=32,332). Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to 1st January 2010, whichever came first. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. Age was categorized into four groups (< 45 year, 45-59, 60-74, 75+ years). The study period was divided into four sub periods: 1989-94, 1995-99, 2000-2004, and 2005-09. Patients older than 95 years of age (n=43) and cases diagnosed by autopsy (n=44) were excluded from survival analysis, because the information on stage and grade were not available in these cases. Mortality data for 1989-2009 were obtained from Statistics The Netherlands[13]. Post-operative FIGO-stage (1988) was used. Clinical stage was used[14], when surgical stage was unknown. Morphology was coded according to the International Classification of Diseases for Oncology (ICD-O). The different morphology codes were grouped into histological subtypes according to the classification of Blaustein and the classification of the World Health Organization[10;15]. The current study focussed on EEC and included pure and variants as common endometrioid epithelial carcinoma mucinous adenocarcinoma[8;15].

Statistical analyses

Annual incidence and mortality rates for the period 1989-2009 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics The Netherlands. Rates were age-standardised to the European standard population (European Age Standardised Rates (EASR)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). To calculate the 95% CI, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y=ax + b$ where $y = \ln(\text{rate})$ and x = calendar year, then $EAPC = 100 * (e^a - 1)$). Incidence rates were also calculated per age group and stage.

Traditional cohort-based relative survival analysis was used for the period 1989-2003

which represents the survival of patients diagnosed during 1989-2003. Since follow-up was available until January 2010, period-based relative survival analysis was used for the most recent period 2004-2009, which gives the most up-to-date estimates[16]. Relative survival estimates were derived as ratios of the observed survival of the EEC patients and the expected survival of the underlying general population with a similar sex and age distribution[17]. Survival trends were evaluated by a linear regression model of annual survival rates. A *p value* <0.05 is considered statistically significant. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses.

Results

In The Netherlands, 32,332 women were diagnosed with a corpus uteri malignancy during the period 1989-2009. The majority of women had EEC (n=25,804, 80%) (Table1). Of women with EEC, 45% were between 60 and 74 years of age and 26% were 75 years or older. The stage distribution in women with EEC was 77-78% stage I, 8-9% stage II, 6-7% stage III and 3-4% stage IV (Table 1). A significant increase in EEC was found comparing the years 1989-94 to 2005-09 (chi-square test, p<0.001). A significant increase of grade I&II and decrease of grade III was seen over the time (p<0.004).

Trends in incidence

Figure 1 shows the trends in the European age-standardised incidence rate (EASR) of corpus uteri malignancy by morphology group. The greatest rise the EASR occurred in patients with EEC, with a significant increase from 11/100,000 person-years in period 1989-94 to 15/100,000 in the last period (EAPC=1.6% (95% CI:1.1, 2.0)). The absolute annual number of women diagnosed with EEC increased from 934 in 1989 to 1518 in 2009. The number of women with NEEC decreased from an average of 430 per year before 1994 to an average of 315 per year after 1994 and the ESR decreased from 23/100,000 in 1989-94 to 12/100,000 2005-09. The incidence of sarcomas remained stable (ESR between 4.5 and 5.2/ 100,000)**.**

A significant increase in the EASR is seen over time in the age group 60-74 (EAPC 2.1% (95% CI: 1.6, 2.6) and in the age group 75 years and older (figure2) . Since 2002, the EASR at group 60-74 surpassed the EASR in the age group of 75 years and older. The EASR increased the most in the FIGO stage I (EAPC 2.2 %; 95%CI 1.6,2.8) (Figure 3a) mainly due to the increase in FIGO stage IB (data not shown). The increase in women with FIGO stage I was the greatest at age 60-74 and also at age 50-59 and 75+ a significant increase was seen (Figure 3b). Figure 3c shows that the advanced FIGO stages IIIB and IV occurred more often in the older age group, as we observed that 10% of the patients of 45-59 years had advanced stages compared to 20-22% of patients 75 years and older. The incidence of the stage III remained stable, while stage IV increased slightly over the time. The EASR concerning the

Table 1 Characteristics of women with endometrioid endometrial carcinoma (EEC) by period of diagnosis in The Netherlands 1989-2009

	Period of diagnosis N (%)								
	1989-1994		1995-1999		2000-2004		2005-2009		p-value
Median age (p10-p90)	67	(52-82)	67	(52-82)	66	(53-82)	66	(54-83)	**0.002**[1]
Age (years)									**<0.001**[2]
< 45	158	2.8	95	1.6	128	1.9	140	1.8	
45-59	1460	25.7	1638	28.3	2002	29.7	2092	27.6	
60-74	2591	45.5	2535	43.7	2940	43.7	3426	45.2	
≥ 75	1480	26.0	1528	26.4	1665	24.7	1926	25.4	
FIGO stage									**0.03**[3]
I	4421	77.7	4442	76.6	5250	78.0	5938	78.3	
II	459	8.1	510	8.8	592	8.8	643	8.5	
III	390	6.9	397	6.8	450	6.7	442	5.8	
IV	219	3.8	206	3.6	232	3.4	290	3.8	
unknown	200	3.5	241	4.2	211	3.1	271	3.6	
Grade									**0,004**[4]
I&II	4361	76.7	4525	78.1	5274	78.3	5979	78.8	
III	972	17.1	921	15.9	1005	14.9	1117	14.7	
unknown	356	6.3	350	6.0	456	6.8	488	6.4	
Total number	**5689**		**5796**		**6735**		**7584**		**25,804**

[1] Significant Kruskal-Wallis test due to younger median age;
[2] Chi-square test significant for change in age distribution over time;
[3] Chi-square test significant because of decrease of unknown stages, without unknown stages p=0.15;
[4] Chi-square test significant change over time increase of grade I&II and decrease of grade III;
Source: The Netherlands Cancer Registry

grade distribution showed an increase in grade 1&2 EEC, which is significant for all ages The EAPC for grade 1&2 is significant: 1.80 (1.32-2.29) . In the age group of 75 years and older the proportion of women with grade 3 histology was the greatest.

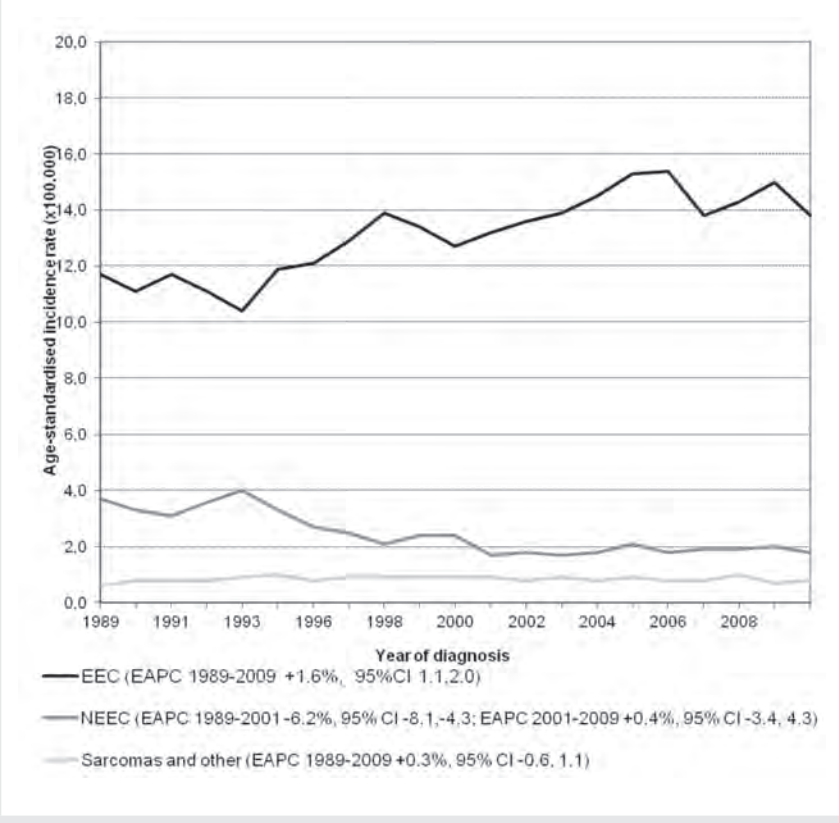


Figure 1 European age-standardised incidence rate (EASR) of corpus uteri carcinoma by subsite: endometrioid endometrial carcinoma (EEC), non-endometrioid endometrial carcinoma (NEEC) and Sarcomas and other in The Netherlands, 1989-2009

EAPC = estimated annual percentage change; EEC= endometrioid endometrial carcinoma; NEEC=non-endometrioid endometrial carcinoma. CI=confidence interval. Source: The Netherlands Cancer Registry

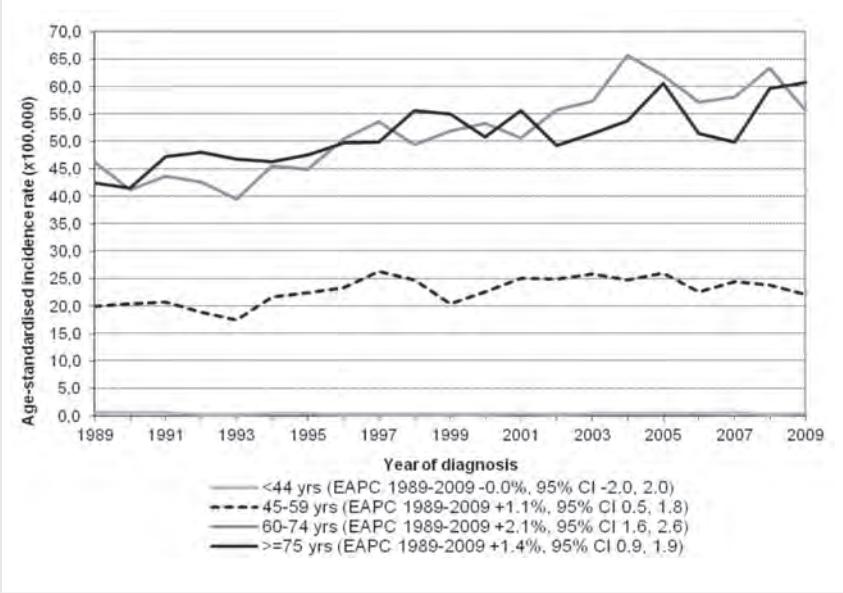
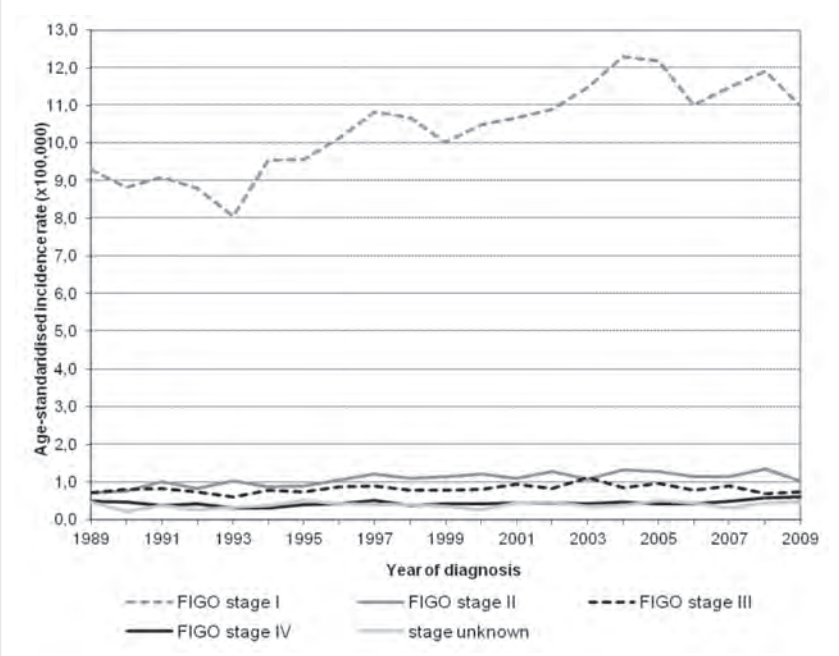


Figure 2 European age-standardised incidence rates (EASR) of endometrioid endometrial cancer (EEC) by gender and age groups in The Netherlands, 1989-2009

EAPC = estimated annual percentage change; CI=confidence interval
Source: The Netherlands Cancer Registry

Trends in survival

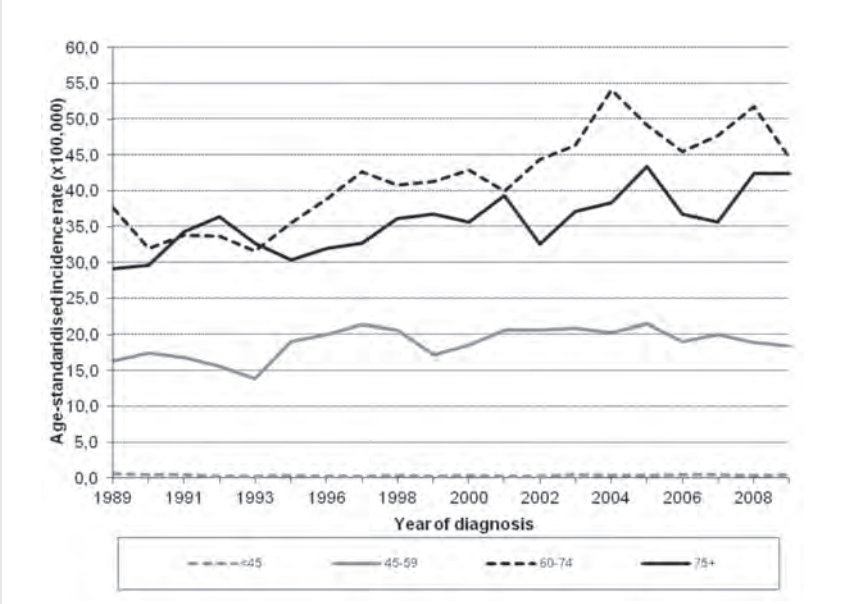
A significant five year relative survival improvement from 83% in 1986-94 to 85% in 2005-09 ($p< 0.001$) is defined as Pr-Surv according to the definition of progress against cancer (Table 2). Furthermore table two lists the five-year relative survival per period according to age, stage and grade. The greatest increase in five-year relative survival was from 82% in women at age group 60-74 in 1989-94 to 87% in 2005-09 ($p<0.001$)). The increase over the time was 90% for FIGO stage I in 1989-94 to 94% in 2005-09 ($p<0.001$) and for grade 1&2 from 89% to 93% ($p<0.001$). Even in women with stage IV EEC the relative five-year survival improved from 13% in 1989-94 to 21% in 2005-09. The women of 75 years and older had lower five-year relative survival compared to younger women. For these women, survival increased from 72 % in the first five year period to 76% in the last five year period, a p-trend of 0.01.



	I	II	III	IV	Unknown
EAPC 1989-2009 (%)	**1.6***	**2.2***	0.60	1.4	1.1
(95% CI)	(1.2, 2.1)	(1.3, 3.1)	(-0.4, 1.5)	(0.3, 2.4)	(-0.50, 2.7)

Figure 3a European age-standardised incidence rates (EASR) of endometrioid endometrial cancer (EEC) by gender and age in The Netherlands, 1989-2009

*significant
FIGO= International Federation of Gynecology and Obstetrics staging system; EAPC= estimated annual percentage change
Source: The Netherlands Cancer Registry



FIGO I	<45	45-59	60-74	75+
EAPC 1989-2009 (%)	-0.01	**1.1***	**2.2***	**1.5***
(95% CI)	-2.2, 2.2	0.4,1.8	1.6, 2.8	0.9, 2.0

Figure 3b European age-standardised incidence rates (EASR) of endometrioid endometrial cancer (EEC) by FIGO stage I per age group in The Netherlands, 1989-2009

*significant
FIGO= International Federation of Gynecology and Obstetrics staging system; EAPC= estimated annual percentage change
Source: The Netherlands Cancer Registry

Trends in mortality

The mortality data show a significant decrease from 1989 until 2009 (Figure 4) and the calculated EAPC was -0.9 (95% CI -1.4, -0.30). The joint point analysis showed a stabilisation in mortality at 2.7 per 100,000 from 1992 onwards. So mortality decreased till 1992 and remained stable thereafter. The EAPC for 1992-2009 was -0.6 (95% CI -1.4, 0.1). The EAPC for mortality is lower than the EAPC for incidence(1.6%).

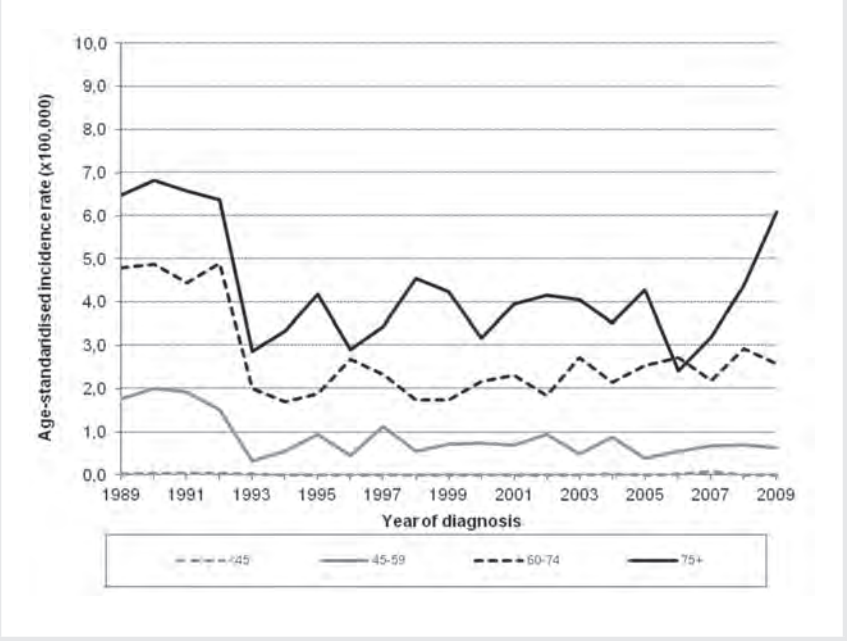


Figure 3c European age-standardised incidence rates (EASR) of EEC (endometrioid endometrial cancer) by FIGO stage IIIB*/IV per age group in The Netherlands, 1989-2009

*1989-1993 IIIA and IIIB were not separated
FIGO= International Federation of Gynecology and Obstetrics staging system
Source: The Netherlands Cancer Registry

Comments

A significant increase in the incidence of corpus uteri malignancies in The Netherlands has been observed because of the rise in incidence of women with EEC. The overall 5-year relative survival increased from 83% to 85% over the past 21 years. The most important reasons for this increase are the increased incidence in FIGO stage I and the increased incidence in EEC tumours with grade1&2. In addition, the decreased incidence in the age group of 75 years and older, with generally lower survival rates, led to improvement in the overall relative survival. Mortality decreased till 1992 and remained stable thereafter(fig 4).

Influences of shifts in the prevalence of risk factors

The observed increase of EEC does not seem to be related to screening or greater awareness, and only a small increase can be explained by a shift in the morphology

Table 2 Five year relative survival of women with endometrioid endometrial carcinoma (EEC) according to period, age, stage and grade in The Netherlands 1989-2009.

	Period of diagnosis								
	1989-1994		1995-1999		2000-2004		2005-2009		p-value
	5-year RS[1]	SE[2]	5-year RS[1]	SE[2]	5-year RS[1]	SE[2]	5-year RS[1]	SE[2]	
Age (years)									
< 45	92	2.3	93	2.7	93	2.4	91	2.5	0.62
45-59	91	0.8	92	0.8	92	0.7	92	0.7	0.43
60-74	**82**	**0.9**	**84**	**0.9**	**87**	**0.8**	**87**	**0.7**	**<0.001[3]**
≥ 75	72	2.0	72	1.9	76	1.8	76	1.7	0.01
FIGO stage									
I	**90**	**0.7**	**93**	**0.6**	**94**	**0.6**	**94**	**0.5**	**<0.001[3]**
II	77	2.6	78	2.5	78	2.2	82	2.1	0.04
III	54	3.0	48	2.9	54	2.7	55	2.6	0.69
IV	13	2.6	8	2.1	19	2.8	21	2.8	n.a.[4]
unknown	55	4.6	31	3.7	39	4.0	35	3.5	n.a.
Grade									
1&2	**89**	**0.7**	**91**	**0.7**	**93**	**0.6**	**93**	**0.6**	**<0.001[3]**
3	60	1.9	56	1.9	58	1.8	61	1.7	0.53
unknown	70	3.1	63	3.1	65	2.7	65	2.6	0.50
overall	**83**	**0.7**	**84**	**0.7**	**86**	**0.6**	**85**	**1.0**	**<0.001[3]**

[1] Rs= relative survival; [2] SE=standard error; [3] significant change p-trend < 0.001;[4] n.a.=not applicable at n<10
Source: The Netherlands Cancer Registry

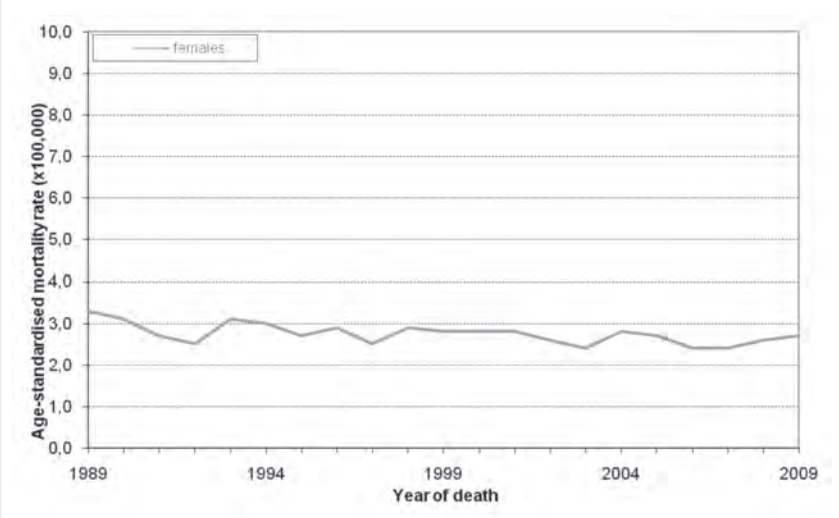


Figure 4 Mortality rate of corpus uteri carcinoma in The Netherlands, 1989-2009

EAPC (estimated annual percentage change) 1989-2009: -0.9 (95% CI -1.4,-0.3)
EAPC 1992-2009: -0.6 (95% CI -1.4, 0.1). Joint point analysis: trend is stable since 1992
Source: The Netherlands Cancer Registry

distribution. Between 1989 and 2009 major shifts occurred in the prevalence of risk factors and it is likely that these changes are related to the increase in the number of women with EEC. Risk factors for EEC include increased age, oral contraceptive use, increased age at first childbirth, nulliparity, polycystic ovary syndrome (PCOS), estrogen exposure from hormone replacement therapy and tamoxifen, and obesity[3]. In The Netherlands, one of the demographic shifts[13] observed between 1989 and 2009 was an increase in the number of women of 65 years and older, however, this is corrected for in the EASR. Another marked influence on the Dutch population was the large-scale introduction of the oral-contraceptive pill in the 1970s[13]. In 1975 the percentage of Dutch women using oral conceptives was the highest of the world. The birth rate decreased after 1970 from 3 to 1.6 in 2009, and the average age for the first childbirth increased from 22 in 1970 to 29.5 in 2009. As a consequence of delaying the first pregnancy, the number of women with reproductive disorders increased[18]. In summary, while the pill itself protects against endometrial cancer, its use leads to lower birth rate, higher age of first childbirth, and increased incidence of nulliparous women, which altogether lead to increased risk for endometrial cancer.

The limited HRT and tamoxifen use in The Netherlands, only partly explains the increase in incidence of EEC[19;20]. There is a need for more specific calculation of the population attributable risk (PAR)[21] of tamoxifen on developing endometrial carcinoma in the Dutch population.
The strongest association for the enhanced EC risk is obesity. Excess weight leads to increased adipose tissue. In adipose tissue, androgens are converted to estrogen, leading to increased endogenous estrogen exposure[5]. In The Netherlands, the percentage obese adults increased from 6 % in 1990 to 13% in 2010[13;22]. Excess body weigh leads to an enhanced EEC risk, which partly explains the increase of EEC in the investigated population.

Changes in the Dutch EEC group in an international perspective
The world standardised ratio's (WSR) for corpus uteri malignancies in the developed world are estimated to be 13/100,000[1]. The incidences of corpus uteri cancers in European countries are lower than the incidence in USA. When the incidences in The Netherlands (15/100,000, 2009)[23] and in the UK (16/100,000, 2006)[6] and in Norway (16/100,000, 2001-2010)[24] are compared to the incidence in USA (24/100,000, 2002-2006)[25] the difference is obvious. Parallel to this is the observation of a high incidence of obesity in the USA, which is much higher than that of The Netherlands and Western Europe; 35% of female adults in the USA are obese[25], compared to 14% of female adults in The Netherlands[22]. Interestingly, the incidence of obesity in the USA has stabilized over the past decade, as has the incidence of EEC. In contrast, obesity rates are increasing in The Netherlands[22], together with the incidence of EEC. Survival and mortality rates for The Netherlands are comparable to those in the United States and Western Europe, where the overall five year survival estimates are between 83 and 89% for corpus uteri cancer in 2002[26].

Remarks on progress against EEC
The interpretation of the improved survival is limited, because the information about treatment is lacking and the changes in survival due to improved treatment are not taken into account. In this study it is assumed that the incidence of EEC significantly increased between 1989-2009 especially in FIGO stage I and in grade 1&2, which influenced the survival rate. In this study EAPC for incidence is much higher than the EAPC for mortality. However, decrease in mortality rates reflect the risk of cancer death among patients diagnosed over the preceding years (e.g. breast cancer mortality rate reflects deaths from the preceding 15-20 years)[9].

Conclusion

The progress against EEC was less than assumed previously, mainly because the incidence has been increasing. Although survival improved, mortality decreased till 1992 and remained

stable thereafter. The strongest associated risk factor for EEC is obesity, which concomitantly increased in The Netherlands. Tackling the growing problem of obesity and physical inactivity is a challenge and warrants attention, for example, increasing numbers of obese women may need a total hysterectomy, preferably with minimal invasive surgery.

Reference List

(1) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61(2):69-90.

(2) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127(12):2893-2917.

(3) Amant F, Moerman P, Neven P, Timmerman D, Van LE, Vergote I. Endometrial cancer. Lancet 2005; 366(9484):491-505.

(4) Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. Curr Oncol Rep 2011; 13(1):71-76.

(5) Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002; 11(12):1531-1543.

(6) Evans T, Sany O, Pearmain P, Ganesan R, Blann A, Sundar S. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. Br J Cancer 2011; 104(9):1505-1510.

(7) Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983; 15(1):10-17.

(8) Boll D, Verhoeven RH, Aa van der M.A., Coebergh JW, Doorn van H.C. Incidence and survival trends of uncommon corpus uteri malignancies in the Netherlands, 1989-2008. Int J Gynecol Cancer 2012; 22:599-606.

(9) Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de VE. Progress against cancer in the Netherlands since the late 1980s: An epidemiological evaluation. Int J Cancer 2011.

(10) Tavassoli F.A., Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. WHO 2003.

(11) Hermanek P, Hutter R, Sobin L, Wagner G, Wittekind. TNM atlas. Springer-Verlag 1997.

(12) Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol 1993; 22(3):369-376.

(13) Statistics Netherlands. http://statline.cbs.nl/StatWeb. Accessed January 2011.

(14) Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet 2008; 101(2):205-210.

(15) Robert J.Kurman. Blaustein's Pathology of the Female Genital Tract. sixth edition 2011.

(16) Brenner H, Arndt V, Gefeller O, Hakulinen T. An alternative approach to age adjustment of cancer survival rates. Eur J Cancer 2004; 40(15):2317-2322.

(17) Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. Eur J Cancer 2011; 47(14):2202-2210.

(18) IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization IAfRoC. Combined estrogen-progestogen contraceptives and combined estrogen-progestogen menopausal therapy. IARC Monogr Eval Carcinog Risks Hum 2007; 91:1-528.

(19) van Herk-Sukel MP, van de Poll-Franse LV, Voogd AC, Nieuwenhuijzen GA, Coebergh JW, Herings RM. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis. Breast Cancer Res Treat 2010; 122(3):843-851.

(20) de Jong-van den Berg LT, Faber A, van den Berg PB. HRT use in 2001 and 2004 in The Netherlands--a world of difference. Maturitas 2006; 54(2):193-197.

(21) Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer 2010; 46(14):2581-2592.

(22) Blokstra A, Vissink P, Venmans LMAJ, Holleman P, van der Schouw YT . Measuring The Netherlands 2009-2010: Monitoring of risk factors in the general population. RIVM Report 260152001/2011 2012.

(23) Online Cancer Registry. www cijfersoverkanker nl 2011.

(24) Trovik J, Mauland KK, Werner HM, Wik E, Helland H, Salvesen HB. Improved survival related to changes in endometrial cancer treatment, a 30-year population based perspective. Gynecol Oncol 2012.

(25) Duong LM, Wilson RJ, Ajani UA, Singh SD, Eheman CR. Trends in endometrial cancer incidence rates in the United States, 1999-2006. J Womens Health (Larchmt) 2011; 20(8):1157-1163.

(26) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55(2):74-108.

2.2

Reduced adjuvant radiotherapy based increasingly on evidence-based treatment of patients with endometrioid endometrial carcinoma resulting in similar survival rates in the Netherlands between 1994 and 2009

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Abstract

Background

Objectives

The aim of this study was to analyse the trends between 1994 and 2009 in primary and adjuvant treatment of women with endometrioid endometrial carcinoma (EEC) according to grade, stage, and age. We paid special attention to the impact on survival of changes in treatment strategies.

Methods

This was a descriptive study of treatment and survival of women with EEC in the Netherlands. Population-based data were extracted from the nation-wide Netherlands Cancer Registry (NCR) between 1994 and 2009. Treatment was described as percentages per age group and period of diagnosis. Five-year relative survival estimates were calculated for three periods using traditional cohort-based analyses. Multivariable survival analyses were performed to estimate the relative excess risk (RER) of death for the periods of diagnosis adjusted for follow-up interval and stratified for FIGO stage.

Results

Between 1994 and 2009, a total of 20 386 women were diagnosed with EEC, the majority of whom had stages IB and IC. We observed a significant decrease in adjuvant radiotherapy (RT) for stage I in the 45-59 age group, while a significant increase in adjuvant RT occurred in stage IC for the age groups of 60 years and older. From 2007, there was a trend towards more adjuvant RT in stage I EEC for the 80+ age group. For stages I and II the five-year relative survival rate did not change during the period under investigation. Known prognostic factors such as age and grade had a significant influence on RER and survival.

Conclusion

Significantly less adjuvant RT was administered in stage I EEC between 1994 and 2009 without this influencing survival. The successful implementation of the results of RCT PORTEC-1 led to a reduction of overtreatment. The introduction of the results of PORTEC-2 led to a reduction of under treatment in elderly patients by replacing external beam RT with vaginal brachytherapy in intermediate risk EEC.

Background

In Europe, malignancy of the corpus uteri is the fourth most common cancer in women. It accounts for approximately 5% of all malignancies and is the eighth leading cause of cancer deaths[1]. In the Netherlands there were 1930 new cases in 2010. The majority (80%) of the corpus uteri malignancies are endometrioid endometrial carcinomas (EEC). The past decades witnessed an increasing incidence in EEC and the five- year relative survival rate increased from 82% to 85%[2].

The past decades witnessed an increase in evidence-based guidelines based on outcomes of randomised trial and its implementation changed treatment strategies (Table 1). In the Netherlands these changes started in the 1980s as knowledge of the biologic behaviour of EEC and prognostic significance of factors such as depth of myometrial invasion, histologic grade, and age, increased. Although retrospective studies showed that the prognosis of patients with early stage EEC, who had been treated with surgery and adjuvant radiotherapy (RT), was excellent[3,4], these studies lacked a control group. A retrospective study on postoperative RT stage I EEC[5] reported no effect on survival, but found a wide variation in referral patterns among gynaecologists from different hospitals, due to differences of opinion about the value of adjuvant RT. Due to the results of the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC -1) randomised controlled trial (RCT)[6] postoperative radiotherapy was abandoned in low risk patients. The subsequent randomised PORTEC-2 trial (2000-2004) showed that external beam radiotherapy could be safely replaced by vaginal brachytherapy that was associated with fewer side effects (Table 1).

The aim of the current study was to analyse the trends in primary and adjuvant treatment of women with endometrioid endometrial carcinoma (EEC) according to grade, stage, and age at diagnosis between 1994 and 2009 in the population based Netherlands Cancer Registry (NCR), and the impact changes in treatment strategies had on survival and relative excess risk of death (RER).

Methods

Setting and participants

This was a descriptive study of treatment and survival of women with EEC in the Netherlands. Population-based data on treatment and survival were extracted from the nation-wide Netherlands Cancer Registry (NCR). All patients with EEC (International Classification of Diseases for Oncology: 8140, 8210, 8230, 8380, 8143, 8211, 8255, 8261, 8262, 8263, 8280, 8382, 8383)[7] diagnosed between 1994 and 2009 (n = 20,386) were included. Patients older than 95 years (n=43) were excluded from the survival analysis, as well as cases diagnosed by autopsy (n=44), because the data was incomplete. Patients younger

Table 1 Randomised trials establishing the role of adjuvant radiotherapy in low and intermediate risk EEC between 1987 and 2006.

Trial accrual period	No. patients eligibility	Surgery	Randomisation	Loco regional recurrence	Survival
GOG#99 1987-1995[1]	392; stages IB, IC, and stage II occult	TH –BSO[2]	NAT[3] vs. EBRT[4]	12% vs. 3% at 2 years, $P < .01$	86% vs 92% at 4 years, $P = 0.56$
PORTEC-1 1990-1997[1]	714; IB grades 2-3, IC grades 1-2	TH-BSO	NAT vs. EBRT	14% vs, 4% at 5 years $P < .001$	85% vs 81% at 5 year $P = 0.31$
PORTEC-2 trail 2002-2006[1]	427; >60 years, IC grades 2 and 3, IB grade 3, stage 2A, any age > 50% myometrial invasion	TH-BSO	EBRT vs. VBT[5]	2.3% vs, 4.7% at 3.75 years	85% vs. 80% at 5 years $P = .17$

[1] Phase III trial Gynecol Oncol 2004; 92(3):744-751; Randomized control trial Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355(9213):1404-1411. an open-label, non-inferiority, randomised trial. Lancet 2010; 375(9717):816-823. [2] TH-BSO= total hysterectomy with bilateral salpingo-oophorectomy; [3] NAT=no adjuvant treatment; [4] EBRT=external beam radiotherapy; [5] VBT=vaginal brachytherapy

than 45 years (n=396) were excluded, either because data on treatment was incomplete or because of another risk profile due to genetic factors such as lynch syndrome.
We defined four age groups: 45-59, 60-69, 70-79, and 80+ years and divided the study period into three sub-periods: 1994-1999, 2000-2004, and 2005-2009.

Data collection

We collected our data from the nation-wide database of the Netherlands Cancer Registry (NCR), which was established in 1989 and is maintained and hosted by the Comprehensive Cancer Centres[8]. The NCR receives and stores notifications of all newly diagnosed malignancies in the Netherlands. Information on patient characteristics (including gender, date of birth, and tumour characteristics, such as date of diagnosis, sub-site [7], histology, FIGO (International Federation of Gynaecologic Oncology) 1988[9] stage, Tumour Lymph Node Metastasis (TNM) classification[10] and grade and treatment, were obtained routinely from the medical records. We used the post-operative FIGO stage (1988) and if it was unknown we used the clinical stage [9].
Initially, information on vital status was obtained from municipal registries and from 1995 onwards from the nation-wide network of population registries. FIGO (1988) stage I was

divided into stages IA (not invading the myometrium) and IB with < 50% myometrial invasion and stage IC with ≥ 50% myometrial invasion. Information on lymph nodes was extracted from pathology reports. If information on lymph nodes was available it was classified as nodes (pN) known, and as pN unknown if no information was available. We calculated follow-up of vital status of all patients as the time from diagnosis to death or to 1 January 2010. We obtained the mortality data for 1994-2009 from Statistics Netherlands[11].

Statistical analyses

We calculated the annual incidence and mortality rates for the 1994 to 2009 period per 100,000 person-years, using the annual mid-year population size obtained from Statistics Netherlands. Rates were age-standardised to the European standard population, European Age-Standardised Rates (ESR). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval. To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. y=ax + b where y = ln (rate) and x=calendar year, then EAPC=100* (e^a–1)). Incidence rates were also calculated per age group and stage[12]. Treatment was described as percentages per age group and sub-period.

The traditional, cohort-based, relative survival method was used to estimate relative survival rates which were derived as ratios of the observed survival of the EEC patients and the expected survival of the underlying general population with a similar sex and age distribution[13]. Survival trends were evaluated by a Poisson regression model [14]. This model was also used to perform multivariate relative survival analyses to estimate (RER) of death for the period of diagnosis adjusted for follow-up interval, stratified by FIGO stage. Treatment variables like percentage of patients with confirmed lymph nodes in the pathology report were added to investigate the effect of therapy on the RER of death for the period of diagnosis. SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used for the statistical analyses.

Results

In the Netherlands between 1994 and 2009, a total of 20,386 women were diagnosed with EEC (Table 2). The median age of 66 years (range 52-83yr) at diagnosis did not change over time. During the sub-period 2005-2009, the majority of women had stages IB and IC, 41% and 25%, respectively, and grades I and II, 47% and 32%, respectively. Approximately a third of the women, i.e. 30%, was younger than 60 years, 70% was 60 years and older, and 15% was 80+ years. Figure 1 shows the increase in incidence of (FIGO 1988) stages IB and IC from 1994 onwards. Stage II increased slightly over time and higher incidences of stages IC, II, III, and IV were found in the older age groups.

Table 2 Characteristics of the total group of 20 386 patients with endometrioid endometrial cancer (EEC)[1] by period of diagnosis in the Netherlands between 1994 and 2009.

	1994-1999		2000-2004		2005-2009	
Median age (p10-p90)	**67**	**(52-82)**	**66**	**(53-82)**	**66**	**(54-82)**
Age in years						
< 45	112	1.7	122	1.9	135	1.8
45-59	1824	28	1936	30	2025	28
60-69	1904	29	2003	31	2424	33
70-79	1768	27	1620	25	1713	23
≥ 80	880	14	852	13	1068	15
FIGO stage						
I	121	1.9	114	1.7	89	1.2
IA	764	12	740	11	840	11
IB	2545	39	2678	41	3019	41
IC	1570	24	1578	24	1827	25
II	557	8.6	573	8,8	616	8,4
III	435	6.7	424	6.5	427	5.8
IV	227	3.5	223	3.4	282	3.8
unknown	269	4.1	203	3.1	265	3.6
Histologic grade						
I	2485	38	2799	43	3431	47
II	2582	40	2316	36	2372	32
III	1044	16	976	15	1082	15
unknown	377	5.8	442	6.8	480	6.5
Total number	**6488**		**6533**		**7365**	

[1]morphology codes: 8140, 8210, 8230, 8380, 8143, 8211, 8255, 8261, 8262, 8263, 8280, 8382, 8383

Treatment

Radiotherapy

During the study period a consequence of the results of randomized trials important changes in the guidelines for adjuvant radiotherapy occurred (Table 1). We found a significant decrease in adjuvant RT in stages IA and IB for all ages and in stage IC for the 45-59 age group (Figures 2a and 2b), while a significant increase in adjuvant RT occurred

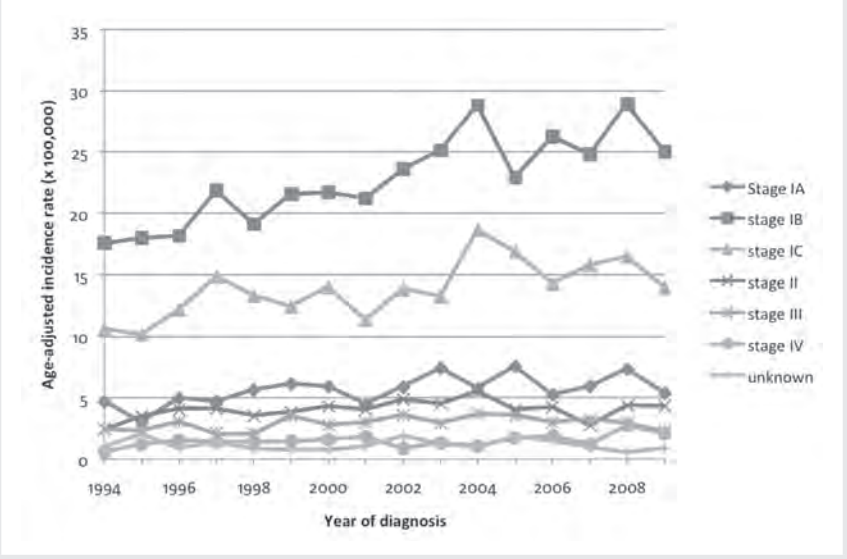

Figure 1 Age adjusted incidence of endometrioid endometrial carcinoma (EEC) according to stage in the Netherlands between 1994 and 2009

FIGO staging system (International Federation of Gynecology and Obstetrics) 1988
Data from Netherlands Cancer Registry

in stage IC for patients of 60 years and older (Figure 2b). Before 2000, 80% of patients received no adjuvant RT and after 2000 this increased to 95%. For women younger than 60 years and stage IC the rate of adjuvant radiotherapy decreased from 65% in period 1994-99 to 30% after 2000. Since 2007, we observed an increasing trend in adjuvant RT in stage I EEC for the 80+ age group (Figures 2a and 2b).

Systemic therapy

In the case of systemic treatment we found a significant increase of adjuvant chemotherapy in stage III (Figures 2c and 2d), while we observed a decreasing trend for administering hormonal therapy in stage IV across all age groups. Furthermore, we observed a significant increase in women who received no therapy in stage IV for all age groups except the 70-79 sub-group.

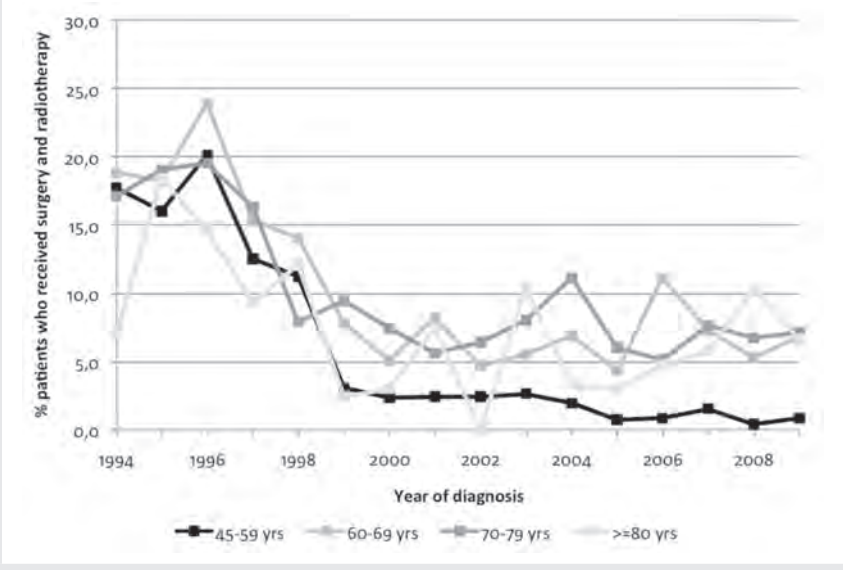

Figure 2a Trends in treatment (surgery and radiotherapy) of endometrioid endometrial carcinoma (EEC) stages IA and IB according to age in the Netherlands between 1994 and 2009

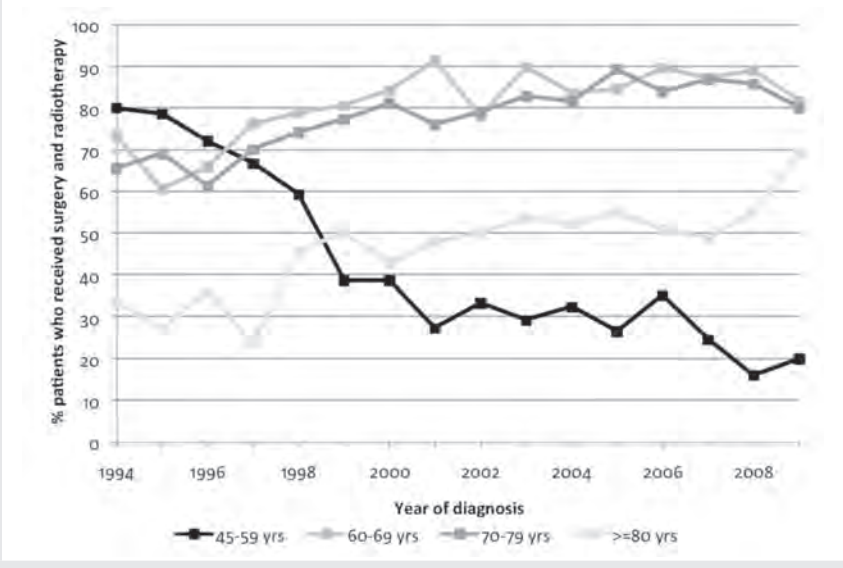

Figure 2b Trends in treatment (surgery and radiotherapy) of endometrioid endometrial carcinoma (EEC) stage IC according to age in the Netherlands between 1994 and 2009

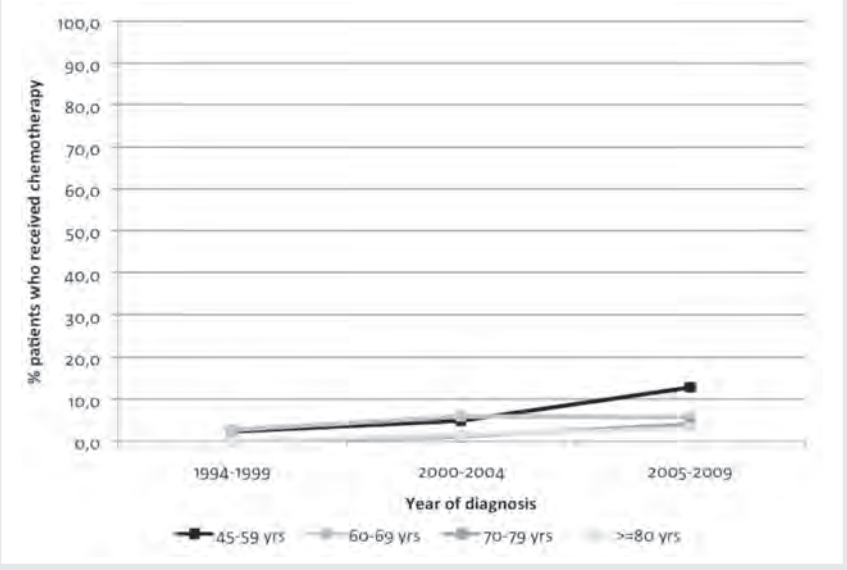

Figure 2c Trends in chemotherapy treatment in endometrioid endometrial carcinoma (EEC) stage III according to age per sub-period in the Netherlands between 1994 and 2009

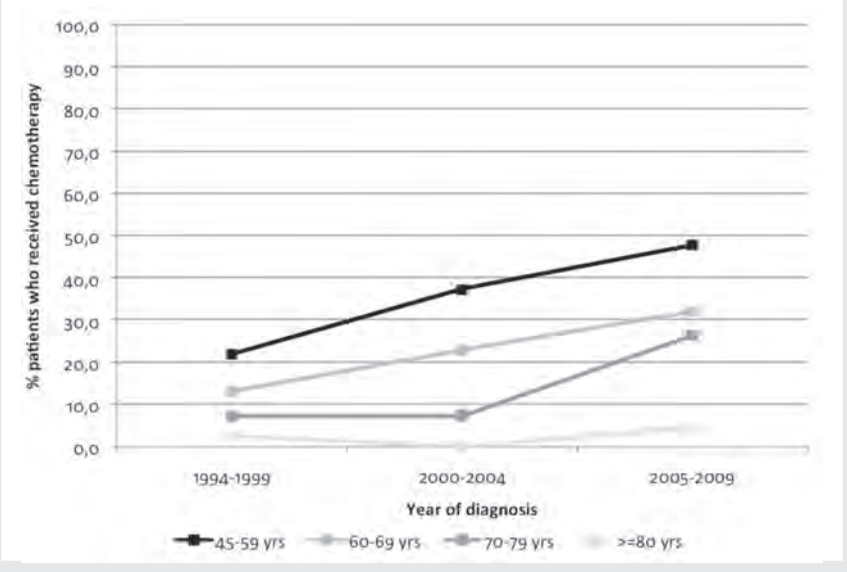

Figure 2d Trends in chemotherapy treatment in endometrioid endometrial carcinoma (EEC) stage IV according to age per sub-period in the Netherlands between 1994 and 2009

Lymph nodes

We observed a slight overall increase in the percentage of pN known (Table 3). A statistical significant increase occurred in pN known in stages I and II for women of 60-69 and 70-79 years of age and in stage IV for the 60-69 age group, but we found no statistically significant increases in any of the other age groups and stages and the absolute numbers are low.

Table 3 Patients with known lymph nodes in pathology report by period, FIGO stage and age in the Netherlands 1994-2009

		45-59		60-69		70-79		80+	
FIGO (1988) stage	**Sub-period**	**N**	**%**	**N**	%	**N**	%	**N**	%
IA-IB	1994-1999	1408	7	1155	6	890	4	350	4
	2000-2004	1351	9	1185	8	771	8	315	2
	2005-2009	1416	10	1439	9	798	11	395	6
	P value		***0.03***[1]		***0.004***		***<0.001***		*0.26*
IC	1994-1999	334	10	629	7	653	6	279	5
	2000-2004	322	9	575	7	563	6	267	4
	2005-2009	339	11	700	11	599	11	316	4
	P value		*0.56*		***0.02***		***0.003***		*0.35*
II	1994-1999	155	20	190	13	214	7	108	6
	2000-2004	161	12	192	14	158	6	107	5
	2005-2009	184	21	195	21	191	16	122	6
	P value		*0.79*		***0.04***		***0.002***		*0.94*
III	1994-1999	123	20	136	15	167	10	83	5
	2000-2004	126	19	134	13	127	12	73	3
	2005-2009	106	18	142	20	100	12	83	6
	P value		*0.76*		*0.25*		*0.62*		*0.71*
IV	1994-1999	47	21	50	16	63	22	24	8
	2000-2004	40	30	41	15	66	17	24	13
	2005-2009	45	36	79	34	75	29	31	19
	P value		*0.13*		***0.01***		*0.29*		*0.24*

[1]Bold figures are significant

Survival

Figure 3a shows that the five-year relative survival rate did not change over time for stages I and II. They remained at the high level of 95% for stages IA and IB, at 90% for stage IC, and

79% for stage II. For women with stages III and IV we observed a significant increase (Figure 3a) from 18% in the 2000-20004 sub-period to 57% in the 2005-2009 sub-period. In the 2005-2009 period the five year survival was 92% for grades 1 and 2 and 61% for grade 3. Figure 3c shows an improvement in survival for the 80+ age group.
We found no changes in the estimated RER of death in FIGO stages IA and IB, stage IC, and stage II (Table 4a). In stage III we observed an improvement in univariate analysis over time, but not in the multivariate analysis (Table 4b), while in stage IV a significant reduction in the RER of death was found over time. A significant decrease of the RER of death for adjuvant RT was seen for stages IC, II ,III, and IV if corrected for age, grade, and sub-period. For stages III and IV a significant advantage of pN known was observed. We found a significant benefit for hormonal therapy in stage IV after correcting for age, grade, and sub-period, while this was not found for chemotherapy.

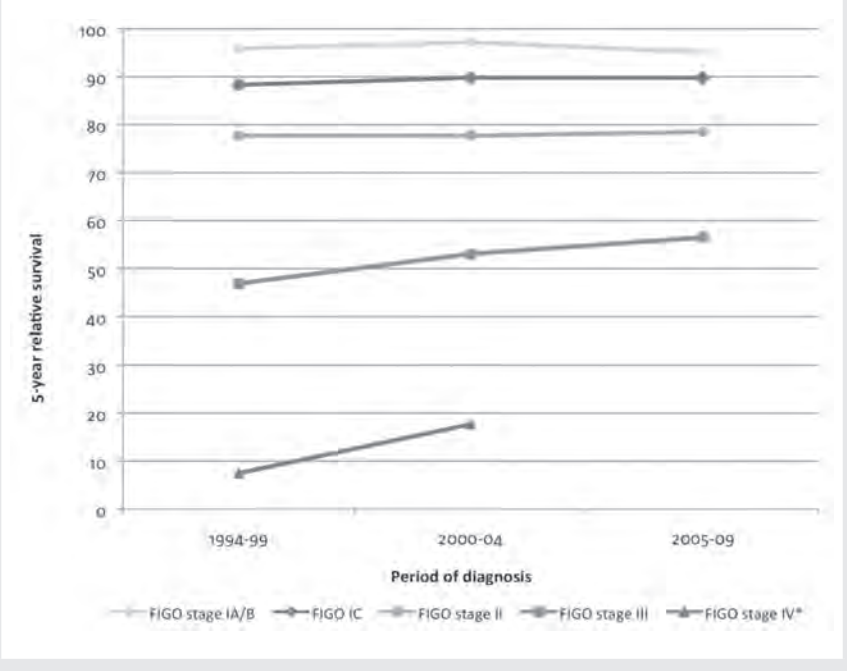

Figure 3a The five-year relative survival rate of women with endometrioid endometrial carcinoma (EEC) according to the FIGO stages during three sub-periods in the Netherlands between 1994 and 2009

* FIGO stage IV estimate of 5-year survival rate for 2005-09 is not given because the number of patients were less than 10 after 5 years of diagnosis

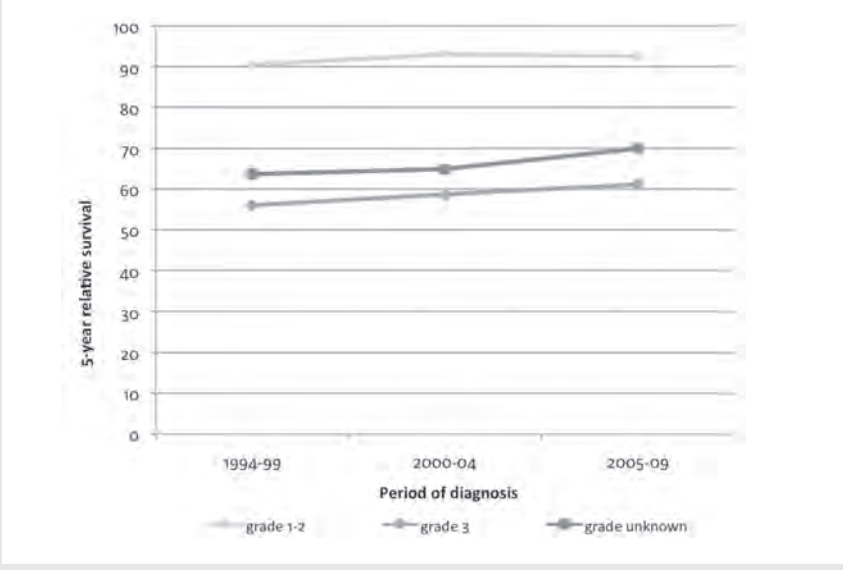

Figure 3b The five-year relative survival rate of women with EEC according to grades during three sub-periods in the Netherlands between 1994 and 2009

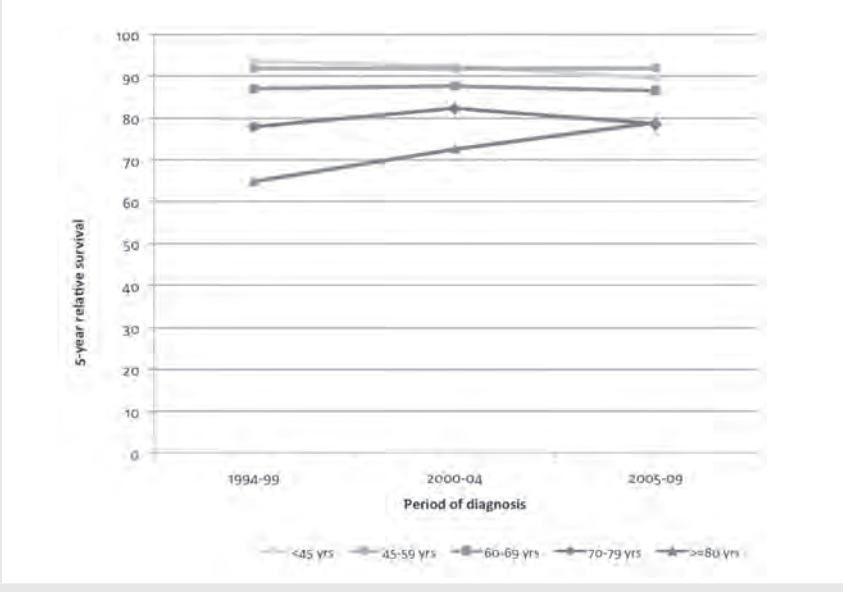

Figure 3c The five-year relative survival rate of women with EEC according to age groups during sub-periods in the Netherlands between 1994 and 2009

Table 4a Univariate and multivariate analyses of relative excess risk (RER) of death by sub-period, age , grade, and pathology of lymph nodes available for FIGO stages IA and IB (<50% myometrial invasion) EEC, stage IC EEC (≥ 50% myometrial invasion) and stage II in the Netherlands between 1994 and 2009.

	FIGO (1988) stages IA and IB				FIGO (1988) stage IC				FIGO (1988) stage II			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Variable	**RER[1]**	**95% CI[2]**	**RER**	**95% CI**	**RER**	**95% CI**	**RER**	**95% CI**	RER	**95% CI**	**RER**	**95% CI**
Period												
1994-1999	1		1		1		1		1		1	
2000-2004	0.84	0.60-1.16	0.80	0.60-1.08	0.91	0.58-1.42	0.91	0.63-1.32	0.98	0.70-1.36	0.99	0.73-1.34
2005-2009	0.95	0.66-1.38	0.88	0.63-1.21	1.03	0.60-1.75	0.85	0.53-1.35	0.80	0.54-1.19	0.74	0.51-1.06
Age												
45-59	1		1		1		1		1		1	
60-69	0.96	0.67-1.38	1.15	0.79-1.66	**1.78**	1.16-2.72	**1.83**	1.20-2.78	**1.71**	1.16-2.54	**1.73**	1.16-2.58
70-79	**1.43[3]**	1.00-2.05	**1.99**	1.40-2.84	**2.41**	1.45-4.00	**2.44**	1.54-3.87	**2.20**	1.48-3.27	**2.26**	1.52-3.36
80+	**1.82**	1.08-3.10	**2.04**	1.23-3.37	1.77	0.43-7.34	**3.23**	1.66-6.30	**2.93**	1.85-4.64	**3.16**	2.04-4.88
grade												
1&2	1		1		1		1		1		1	
3	**5.37**	4.04-7.12	**5.45**	4.13-7.19	**7.82**	5.38-11.36	**7.14**	4.96-10.27	**3.84**	2.86-5.16	**3.71**	2.80-4.90
unknown	**2.84**	1.52-5.32	**3.13**	1.75-5.61	**3.21**	1.69-6.10	**3.50**	1.99-6.17	**2.68**			
Surgery and RT												
no	1				1				1			
yes	3.12	2.05-4.75			0.77	0.57-1.03			**0.43**	0.32-0.57		

[1]RER= relative excess risk of death, [2] CI= confidence interval, [3]Bold figures are significant

Table 4b Univariate and multivariate analysis of relative excess risk (RER) of death by sub-period, age group, grade, and pathology of lymph nodes available for FIGO stages III and IV EEC in the Netherlands between 1994 and 2009.

	FIGO (1988) stage III				FIGO (1988) stage IV			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	**RER[1]**	**95% CI[2]**	**RER**	**95% CI**	**RER**	**95% CI**	**RER**	**95% CI**
Period								
1994-1999	1		1		1		1	
2000-2004	0.82	0.66-1.02	0.84	0.68-1.03	**0.75**	0.61-0.93	**0.71**	0.57-0.87
2005-2009	**0.77[3]**	0.60-0.99	0.83	0.65-1.05	**0.64**	0.52-0.79	**0.63**	0.51-0.77
Age								
45-59	1		1		1		1	
60-69	**1.58**	1.17-2.13	**1.51**	1.12-2.03	**1.62**	1.25-2.11	**1.72**	1.32-2.25
70-79	**2.68**	2.02-3.55	**2.43**	1.83-3.23	**1.73**	1.35-2.22	**1.82**	1.42-2.33
80+	**3.95**	2.92-5.35	**3.38**	2.49-4.59	**2.22**	1.67-2.94	**2.34**	1.75-3.11
grade								
1&2	1		1		1		1	
3	**3.57**	2.89-4.40	**3.19**	2.61-3.90	**1.75**	1.44-2.14	**1.78**	1.46-2.17
unknown	**3.56**	2.55-4.97	**3.06**	2.22-4.23	**1.73**	1.35-2.22	**1.67**	1.30-2.14
pN								
unknown	1				1			
known	**0.60**	0.42-0.86			**0.59**	0.44-0.79		
Surgery + radiotherapy								
no	1				1			
yes	**0.42**	0.35-0.51			**0.35**	0.26-0.47		
Hormonal therapy								
no					**1**			
yes					0.82	0.67-0.99		

[1]RER= relative excess risk of death, [2]CI= confidence interval, [3]Bold figures are significant

Discussion

Radiotherapy

Adjuvant RT in FIGO stage I EEC was administered significantly less between 1994 and 2009 without this having an effect on survival. This reduction can be directly explained by the changes in the indications for adjuvant radiotherapy in this period. In the late 1980s and beginning of 1990s, the growing awareness amongst Dutch radiation oncologists and gynaecologists of possible overtreatment of patients with low and intermediate risk EEC led to nation-wide cooperation in the PORTEC-1 trial. As a result of the PORTEC-1 trial, adjuvant radiotherapy remained only indicated for stage I EEC when two out of three risk factors are positive, i.e. > 50% invasion in the myometrium, grade III, and age over 60 years. Although the results of this trial were published in 2000, we observed that the decline in adjuvant RT for EEC already started in 1996. This was perhaps due to the large number of specialist participating and their awareness of possible overtreatment. Stabilisation commenced in 2000 after PORTEC-1 was published and continued after the adjustment of the Dutch oncology guidelines in 2004[15]. In the meantime, the randomized Gynecolgic Oncology Group (GOG) trial[16] published in 2004, in which all patients underwent a staging lymphadenectomy, confirmed the results of the PORTEC-1 trial and the abandonment of adjuvant radiotherapy in low risk EEC patients. Conclusions of PORTEC-1 and the GOG #99 are that risk factors can be applied to select Stage I patients with the highest risk of recurrence. Despite the significant improvement of loco regional control, there was no survival advantage and a considerable cost of gastrointestinal toxicity[17]. Nevertheless, in this analysis, after correction for grade, sub-period, and age, a significant advantage of RT was found for stages IC, II,III and IV. The results of the RCT PORTEC-2[18], stating that vaginal brachytherapy (VBT) had fewer toxic effects and was recommended as treatment of choice in stage I EEC patients with risk factors. From 2007 onwards, we found an increase in adjuvant RT in the age group of 80+ years due possibly to the implementation of PORTEC- 2 as VBT is better tolerated, especially in elderly patients.

Systemic therapy

The use of adjuvant chemotherapy increased significantly in stage III for the 45-59 age group and for almost all age groups in stage IV(figure 2c and 2d). Numbers are limited, firm conclusions can therefore not be drawn, but , although we found no influence of chemotherapy on the RER of death, the survival of both stages III and IV increased from 1994-2009. Nevertheless, the survival rate for stage IV was only 18%.

Lymph nodes

Another finding was the modest increase of available lymph nodes (pN known) in the pathology reports. Whether to conduct a lymphadenectomy in a patient with EEC is still a matter of debate. Two large randomised trials including low and intermediate risk patients

reported no benefit[19;20] of lymphadenectomy in overall survival or differences in recurrences, while lymphadenectomy was associated with higher rates of treatment-related morbidity like lymphedema of the legs[21]. An increase in number of tumor positive lymph nodes could result in stage migration. We found no argument for stage migration in changes of incidence, and survival remained the same for stage IC, probably the improvement in survival in stage III partly can be explained by stage migration. The overall percentage of known pN was low and therefore no conclusions could be drawn, if this was a result of increased debulking of enlarged nodes or of more frequent staging.

Survival

We observed no changes in the RER of death in stages I, II, and III, but we did observe an improvement for stage IV. As is well known, and confirmed by this analysis, prognostic factors such as age and grade have a pronounced influence on the RER of death and on survival. In EEC, especially in the early stages, survival is excellent and the differences in survival in the older age group compared to the younger age group is due partly to mortality as a consequence of comorbidity with second cancers (breast cancer) or previous cancers, cardiovascular disease, diabetes mellitus, or hypertension[22]. Especially in the population of women with EEC the prevalence of obesity and related comorbidities are known to be increasing[23-25]. The treatments given to these elderly patients need to be assessed against the background of the quality of life, as clearly demonstrated by PORTEC-2, which recommended that VBT be administered in low risk EEC only. Nevertheless, a significant increase in survival was seen in women with stages III and IV EEC, even for the 80+ age group. And, as we concluded before, changes in treatment strategies such as adjuvant chemotherapy cannot explain this improvement. These changes are probably due to improvements in the treatment of comorbidities[26].

Limitations of this population-based study are that we did not register external beam RT or VBT separately nor did we register whether chemotherapy and hormonal therapy were given as primary treatment or as adjuvant therapy. Neither the prognostic factor lymph angio invasion (LVSI) was registered. The conclusions for stages III and IV are weak because they were based on small numbers of patients since only 10% of the population had stages III or IV EEC. This was also the case for pathological assessed lymph nodes.

Conclusion

Between 1994 and 2009, adjuvant RT decreased significantly in stage I EEC without having an effect on survival, due to the successful, nation-wide implementation of the findings of the PORTEC-1 trial. This led to the reduction of overtreatment. Moreover, introduction of the findings of PORTEC-2 possibly led to the reduction of under treatment in elderly patients in intermediate EEC thanks to the introduction of VBT. The importance of the known risk factors like age, stage and grade was confirmed again.

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Reference List

(1) Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer 2013; 49(6):1374-1403.

(2) Boll D, Karim-Kos HE, Verhoeven HA, Burger CW, Coebergh JW, van de Poll-Franse LV et al. Increased incidence and improved survival in endometrioid endometrial cancer diagnosed since 1989 in The Netherlands: a population based study. Eur J Obstet Gynecol Reprod Biol 2013; 166(2):209-214.

(3) Lybeert ML, van Putten WL, Ribot JG, Crommelin MA. Endometrial carcinoma: high dose-rate brachytherapy in combination with external irradiation; a multivariate analysis of relapses. Radiother Oncol 1989; 16(4):245-252.

(4) Meerwaldt JH, Hoekstra CJ, van Putten WL, Tjokrowardojo AJ, Koper PC. Endometrial adenocarcinoma, adjuvant radiotherapy tailored to prognostic factors. Int J Radiat Oncol Biol Phys 1990; 18(2):299-304.

(5) Lybeert ML, van Putten WL, Brolmann HA, Coebergh JW. Postoperative radiotherapy for endometrial carcinoma. Stage I. Wide variation in referral patterns but no effect on long-term survival in a retrospective study in the southeast Netherlands. Eur J Cancer 1998; 34(4):586-590.

(6) Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355(9213):1404-1411.

(7) Tavassoli F.A., Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. WHO 2003.

(8) Online Cancer Registry. www cijfersoverkanker nl 2011.

(9) Odicino F, Pecorelli S, Zigliani L, Creasman WT. History of the FIGO cancer staging system. Int J Gynaecol Obstet 2008; 101(2):205-210.

(10) Wittekind C, Klimfinger M, Sobin L.H. TNM-atlas. UICC global cancer control 2005; 5.

(11) Statistics Netherlands. http://statline.cbs.nl/StatWeb. Accessed January 2011.

(12) Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19(3):335-351.

(13) Hakulinen T, Seppa K, Lambert PC. Choosing the relative survival method for cancer survival estimation. Eur J Cancer 2011; 47(14):2202-2210.

(14) Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004; 23(1):51-64.

(15) Dutch national oncology guidelines. www oncoline nl 2004.

(16) Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004; 92(3):744-751.

(17) Nout RA, van de Poll-Franse LV, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol 2011; 29(13):1692-1700.

(18) Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010; 375(9717):816-823.

(19) Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009; 373(9658):125-136.

(20) Benedetti PP, Basile S, Maneschi F, Alberto LA, Signorelli M, Scambia G et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008; 100(23):1707-1716.

(21) van de Poll-Franse LV, Pijnenborg JM, Boll D, Vos MC, van den Berg H, Lybeert ML et al. Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study. Gynecol Oncol 2012; 127(1):153-160.

(22) Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer 2011; 47(10):1504-1510.

(23) Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005; 55(3):231-240.
(24) Thong MS, Mols F, Verhoeven RH, Liu L, Andrykowski MA, Roukema JA et al. Multiple primary cancer survivors have poorer health status and well-being than single primary cancer survivors: a study from the population-based PROFILES registry. Psychooncology 2012.
(25) Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer 2010; 126(2):490-499.
(26) Askoxylakis V, Thieke C, Pleger ST, Most P, Tanner J, Lindel K et al. Long-term survival of cancer patients compared to heart failure and stroke: a systematic review. BMC Cancer 2010; 10:105.

2.3

Incidence and survival trends of uncommon corpus uteri malignancies in The Netherlands, 1989-2008

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Abstract

Introduction

Corpus uteri cancer is the most common malignancy of the female reproductive tract in industrialized countries and its incidence is increasing. Although the majority of these tumors are of the common endometrial type, there are also many uncommon tumors of the corpus uteri. We examined the incidence and survival of patients with uncommon epithelial tumors, carcinosarcomas and sarcomas of the corpus uteri diagnosed since 1989.

Methods

All common and uncommon malignancies of the corpus uteri registered in the nation-wide population-based The Netherlands Cancer Registry (NCR) during 1989-2008 were included (n=30,960). The histological subtypes were described according to the Blaustein classification system. Age-standardized Incidence for 1989-2008 was calculated per 1,000,000 person-years(p-y), and relative survival was calculated according to the type of uncommon tumor.

Results

The incidence of corpus uteri malignancies increased from 159 to 177 per 1,000,000 p-y, mainly due to the rise in endometrioid adenocarcinomas from 106 to 144 per 1,000,000 p-y; in contrast, incidence of uncommon epithelial endometrial carcinomas (UEEC) decreased from 30 to 13 per 1,000,000 p-y, although carcinosarcomas increased slightly from 5.1 to 6.9 per 1,000,000 p-y. Furthermore, a remarkable shift in incidence of endometrial stromal cell sarcomas (ESS) was observed from high grade ESS to low grade ESS after 2003. Five-year relative survival for patients with UEEC decreased from 72% to 54% and for patients with serous adenocarcinoma from 73% to 51%. Coinciding with an increase in the incidence of common adenocarcinoma of the corpus uteri there was a decline in uncommon adenocarcinomas and a more or less stable incidence of sarcomas and carcinosarcomas.

Conclusion

The decrease in UEEC tumors consisted largely of fewer serous carcinomas, possibly and likely reflecting a more precise histopathological classification of villoglandular tumors. Unfortunately, relative survival for patients with UEEC, sarcomas and carcinosarcomas did not improve over the study period, indicating a need for more research on treatment strategies for this group of patients.

Introduction

Malignancy of the corpus uteri is the most common malignancy of the female genital tract in the western world, with 287,000 new cases being diagnosed and 74,000 patients dying from this disease in 2008 [1]. During the study period 1989-2008 a number of changes occurred in The Netherlands. Demographic changes included the increasing female population (from 7.5 to 8.3 million). Furthermore the greying of the population, with an increase of half million women in the age group 65 years and older [2]. The European standardized (ESR) incidence of corpus uteri malignancies increased from 159 in 1989 to 177 per 1,000,000 patients in 2008[3]. This against a background of women, who postpone the first pregnancy, used oral anticonception and hormone substitution therapy more frequently in the seventies, the eighties and the nineties of the last century and lifestyle changes which cause an increase in obesity[4]. Furthermore the diagnostic facilities underwent progress, especially developments in immunohistochemistry changed the interpretation of histopathology and improved tools to classify tumors. These changes and developments might affect not only the incidence of the common epithelial endometrial carcinomas (CEEC), representing approximately 80% of the invasive malignancies of the corpus uteri, but also the incidence and frequency of the remaining 20% of the unusual epithelial endometrial carcinomas (UEEC), such as serous carcinoma and clear cell carcinomas, as well as carcinosarcomas, sarcomas and unspecified tumors [5]. It has been suggested that these tumors are more likely to occur in women who received tamoxifen for breast cancer, the incidence of the latter increased from 490 to 651 per 1,000,000 p-y in 2008. While CEEC have been studied extensively, there is a scarcity of empirical data on the incidence and survival of patients diagnosed with UEEC and sarcomas. We therefore analyzed time trends in incidence and survival using data from The Netherlands Cancer Registry (NCR) . As far as we know, this is the first study examining differential trends of corpus uteri malignancies on such a large and detailed scale.

Methods

Data collection

Population-based data was obtained from The Netherlands Cancer Registry (NCR). Notification of all newly diagnosed malignancies for the NCR occurred via the automated national, pathological archive (PALGA). Additional sources of data were the national registry of hospital discharge, as well as records obtained from radiotherapy institutions and various laboratories. Information on patient characteristics such as gender, date of birth, and tumor characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology ICD-O-3)[6], histology, stage (tumor Lymph Node Metastasis (TNM) classification) [7] grade, and primary treatment, were obtained from the

medical records. Because registration clerks are thoroughly trained and computerized consistency checks are routinely carried out at regional and national levels, completeness is estimated to be at least 95% [8]. For analyses according to stage, tumors diagnosed after 1993 were used, because the classification of TNM stage of endometrial cancer changed in 1992 [9]. Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to 1st January 2009. The information on vital status was initially obtained from municipal population registries and from 1995 onwards from the computerized nationwide network, providing virtually complete coverage of all deceased Dutch citizens. For the present study, all new primary tumors of the corpus uteri (C54) diagnosed from 1989-2008 in The Netherlands were included (n=30,960). Lymphomas and Kaposi sarcomas were excluded from all analyses. The histological subtypes were defined according to the Blaustein classification system [10], which is derived from the classification of the World Health Organization (Table1)[6]. Histopathological diagnoses were divided into six main groups: Common epithelial endometrial carcinomas (CEEC), Uncommon epithelial endometrium carcinomas (UEEC), Sarcomas, Carcinosarcomas/ Malignant Müllerian Mixed tumor, unclear and "neoplasms not otherwise specified" and a remaining group called "other". The study period was divided into four 5-year periods: 1989-1993, 1994-1998,1999-2003 and 2004-2008. The postoperative stage is used, except for cases without surgery, in which case clinical stage was used.

Statistical analysis

Incidence was calculated per 1,000,000 person-years, using the annual mid-year population size as obtained from Statistics The Netherlands. Rates were age-standardized to the European standard population (European Standardised Rates (ESR)).

For patients with 2 primary corpus uteri tumors (*n*=32), only the first diagnosed tumor was included in the survival analyses. Relative survival is an estimation of the disease-specific survival, being the absolute survival among the corpus uteri cancer patients divided by the expected survival for the general population with the same sex and age structure [11]. Traditional cohort-based relative survival analysis was performed with SAS software (SAS system 9.2, SAS Institute, Cary, NC). Relative survival was calculated for the total group and also according to histology. Groups with less than 10 patients alive 5-years after diagnosis were excluded from 5-year survival estimations.

Results

A total of 30,960 patients with corpus uteri malignancies was diagnosed between 1989-2008. There were 96 different morphology codes that were divided into six major groups (Table 1).

UEEC accounted for 12% of all corpus uteri malignancies during the study period (Table 1). The incidence decreased from 30 to 13 per 1,000,000p-y, mainly caused by the decrease in serous adenocarcinoma (Table 2). Serous carcinoma, also known as uterine papillary serous carcinoma, was the most frequently diagnosed tumor among the UEEC malignancies (68%) followed by clear cell carcinoma (15%), adenosquamous carcinoma (13%), large cell and undifferentiated tumors (0.2%) and sqaumous cell carcinoma (0.2%) (Table 2). Neuroendocrine, transitional cell carcinoma and small cell carcinomas were very rare. The median age of patients with the rarest tumors (< 60 per 1,000,000 p-y) varied between 48 and 79 years. The five-year relative survival of patients with UEEC decreased from 72% in 1989-1993 to 54% in 2004-2008 and from 73% in 1989-1993 to 51% in 2004-2008 for serous adenocarcinomas (Table 3.1).

Sarcomas accounted for 4.2% of all corpus uteri malignancies (Table 1) and their incidence remained stable at about 7 per 1,000,000 p-y (Table 2). The most frequently diagnosed sarcoma was leiomyosarcoma followed by endometrial stromal cell sarcoma (ESS), both high and low grade. Patients with leiomyosarcomas and ESS low grade had a relatively young median age of 55 and 48 years, respectively. While the incidence of all sarcomas did not change, a shift occurred from high to low grade in the ESS group (Table 2). Five-year relative survival was high for patients with low grade ESS (92%). Survival of leiomyosarcoma patients, being 40%, did not improve over the study period.

Carcinosarcomas, formerly known as malignant mixed müllerian tumors, accounted for 3.7% of all corpus uteri malignancies (Table 1). The median age of diagnosis was 71 years, 5 years older than the common epithelial group. The age standardized incidence increased from 5.1 during 1989-1993 to 6.9 per 1,000,000 p-y during 2004-2008 but its five-year relative survival (35%) remained unchanged over time (Table 3.1), being lower for women in the older age group (25%). Figure 1 shows one, three and five-year relative survival with the steepest decline in the first three years after diagnosis in both age groups.

The most common tumor of the CEEC group is the endometrioid adenocarcinoma (EAC). The incidence of EAC increased over time from 105 per 1,000,000 p-y during 1989-1993 to 128 per 1,000,000 p-y during 2004-2008 (Table 2). Patients with EAC with adenosquamous differentiation, mucinous adenocarcinoma and variants of EAC had the same median age (Table1) and about the same five-year relative survival at all ages (Table 3.1). Five-year relative survival for patients with EAC differed between women below 75 years (88%) and women of 75 years and older (74%) (Tables 3.2 and 3.3), this was also found for the other tumor types.

Table 1 Histological classification, ICD-O morphology codes of corpus uteri malignancies, incidence and mean-age of corpus uteri malignancies according to histology in The Netherlands Cancer Registry(NCR) 1989-2008

Morphologic group	ICD-O morphologic codes
Common Epithelial Endometrial Carcinoma (CEEC)	
- Endometrioid Adenocarcinoma (EAC)	8140, 8210, 8230, 8380
- EAC with adenosquamous differentiation	8570, 8572
- Mucinous adenocarcinoma	8480, 8481
- Variants of EAC	8143, 8211, 8255, 8261, 8262, 8263, 8280, 8382, 8383
Uncommon Epithelial Endometrial carcinoma (UEEC)	
- Serous carcinoma	8260, 8441, 8450, 8460, 8461, 8471
- Clear Cell carcinoma	8005, 8310
- Adenosquamous carcinoma	8560
- Large Cell Carcinoma/ Undifferentiated Carcinoma	8012, 8020, 8072
- Squamous Cell Carcinoma	8070, 8071, 8083, 8084
- Small Cell Carcinoma	8041
- Transitional cell carcinoma	8021, 8120
- Neuroendocrine differentiation	8013, 8246, 8574
- Mixed cell adenocarcinoma	8323,8940
Sarcomas	
- Leiomyosarcoma	8890, 8891, 8895, 8896
- Endometrial stromal sarcoma high grade	8930, 8935
- Endometrial stromal sarcoma low grade	8931
- Adenosarcoma	8933
- Sarcoma other/ Not otherwise specified (NOS)	8800, 8801, 8802, 8805, 8810, 8830, 8936, 9220, 9260
- Rhabomyosarcoma	8900, 8901, 8910, 8920
Carcinosarcoma (Malignant Müllerian Mixed tumor)	8381,8950, 8951, 8980, 8990
Type unclear/unspecified	8000, 8001, 8010, 9990
Other	8031, 8033, 8045, 8046, 8141, 8201, 8240, 8320, 8330, 8384, 8573, 8430, 8462, 8490, 8502, 8503, 8680, 8940, 9040, 9071,9104, 9105, 9110, 9473
Total	

	n	%	Median	P25	P75
	24,652	**80%**	**66**	**58**	**75**
	23,467	76%	66	58	75
	811	2.6%	65	57	74
	286	0.9%	68.5	60	77
	88	0.3%	68	58	76
	3,618	**12%**	68	60	76
	2,451	7.9%	68	60	76
	554	1.8%	71	63	78
	471	1.5%	64	56	73
	54	0.2%	65.5	56	79
	52	0.2%	67.5	57.5	74.5
	15	0.1%	74	62	76
	2	<0.1%	74.5	67	82
	12	<0.1%	76	69	82
	7	<0.1%	65	60	71
	1,294	**4.2%**	56	47	68
	702	2.3%	55	47	65
	319	1.0%	59	48	69
	113	0.4%	48	43	55
	78	0.3%	65	51	73
	67	0.2%	66	55	76
	15	0.1%	72	66	79
	1,143	3.7%	71	62	78
	206	0.7%	79	64	85
	49	0.2%	68	56.5	74.5
	30,960	**100%**	66	58	75

Table 2 European age-standardized corpus uteri malignancy incidence rates per 1,000,000 person-years according histology in The Netherlands Cancer Registry 1989-2008.

Morphologic group	Period of diagnosis				
	1989-1993	1994-1998	1999-2003	2004-2008	Total period
Total	**159**	**166**	**166**	**177**	**167**
Common Epithelial Endometrial Carcinoma (CEEC)	**115**	**131**	**138**	**149**	**134**
- Endometrioid Adenocarcinoma (EAC)	106	124	133	144	128
- EAC with adenosquamous differentiation	7.4	4.3	3.4	3.3	4.5
- Mucinous adenocarcinoma	1.7	2.2	1.0	1.0	1.5
- Variants of EAC	0.2	0.1	0.5	0.9	0.5
Uncommon epithelial Endometrial Carcinoma (UEEC)	**30**	**21**	**14**	**13**	**19**
- Serous carcinoma	22	14	7.9	7.1	13
- Clear Cell carcinoma	2.9	2.6	2.6	2.9	2.7
- Adenosquamous carcinoma	4.5	3.4	2.2	0.9	2.6
- Large Cell Carcinoma/ Undifferentiated Carcinoma	0.4	0.3	0.2	0.2	0.3
- Squamous Cell Carcinoma	0.2	0.3	0.3	0.3	0.3
- Small Cell Carcinoma	0.1	0.1	0.1	0.1	0.1
- Transitional cell carcinoma	0.0	0.0	0.0	0.0	0.0
- Neuroendocrine differentiation	0.0	0.0	0.1	0.1	0.1
- Mixed cell adenocarcinoma	0.0	0.0	0.0	0.1	0.0
Sarcomas	**7.0**	**8.0**	**7.9**	**7.3**	**7.6**
- Leiomyosarcoma	4.4	4.9	4.3	3.4	4.2

Source: NCR

Table 2 Continued.

Morphologic group	Period of diagnosis				
	1989-1993	1994-1998	1999-2003	2004-2008	Total period
- Endometrial stromal sarcoma high grade	2.0	2.3	1.8	1.3	1.8
- Endometrial stromal sarcoma low grade	0.0	0.1	0.9	1.4	0.7
- Adenosarcoma	0.1	0.4	0.5	0.7	0.4
- Sarcoma other/Not otherwise specified (NOS)	0.3	0.2	0.4	0.4	0.4
- Rhabomyosarcoma	0.1	0.1	0.0	0.1	0.1
Carcinosarcoma (Malignant Müllerian Mixed tumor)	**5.1**	**5.2**	**5.5**	**6.9**	**5.7**
Type unclear/unspecified	1.4	0.8	0.7	0.7	0.9
Other	0.2	0.3	0.2	0.3	0.3

Source: NCR

Discussion

During 1989-2008 a total of 30,960 patients with corpus uteri malignancies were recorded in the NCR. In all, 3,618 patients diagnosed with UEEC, which is 12% of all corpus uteri malignancies, the age-standardized incidence decreased mainly due to the decline in serous carcinomas after 1994. This can probably be explained by a more accurate differentiation between villoglandular EAC and serous adenocarcinomas, due to progress in histopathological diagnosis[12]. The five-year relative survival for patients with UEEC decreased from 72% to 54%. The main factor that contributed to this is the decrease in survival of patients with serous carcinoma. The age standardized incidence of all sarcomas remained unchanged, although in 2004 a change was observed in the histopathological classification of patients with endometrial stromal cell sarcoma (ESS)[13]. Carcinosarcomas, formerly known as malignant mixed müllerian tumors, accounted for 3.7% of all corpus uteri malignancies. The incidence of carcinosarcomas increased slightly (from 5.1 to 6.9) but without a change in five-year relative survival (35%). Among patients with UEEC and carcinosarcomas five-year survival was low compared to patients with CEEC although improvement has been seen in the past decades.

Table 3.1 Five-year relative survival of patients with corpus uteri malignancy in The Netherlands according to period of diagnosis and morphologic group, The Netherlands Cancer registry 1989-2008

Morphologic group	Period of diagnosis									
	1989-1993		1994-1998		1999-2003		2004-2008		Total period	
	RS	SE	RS	SE	RS	SE	RS	SE	RS	SE
Total	**77%**	**0.7%**	**78%**	**0.7%**	**79%**	**0.6%**	**80%**	**0.7%**	**79%**	**0.3%**
Common Epithelial Endometrial Carcinoma (CEEC)	**82%**	**0.7%**	**84%**	**0.7%**	**86%**	**0.6%**	**86%**	**0.7%**	**85%**	**0.3%**
- Endometrioid Adenocarcinoma (EAC)	82%	0.8%	84%	0.7%	86%	0.6%	86%	0.7%	85%	0.3%
- EAC with adenosquamous differentiation	85%	2.8%	89%	3.5%	84%	3.9%	91%	4.0	87%	1.7%
- Mucinous adenocarcinoma	77%	6.2%	89%	5.1%	84%	7.2%	100%	6.8%	87%	3.1%
- Variants of EAC	*n*<10		*n*<10		97%	6.2%	88%	5.0%	79%	5.8%
Uncommon epithelial Endometrial Carcinoma (UEEC)	**72%**	**1.6%**	**67%**	**1.9%**	**58%**	**2.2%**	**54%**	**2.7%**	**64%**	**1.0%**
- Serous carcinoma	73%	1.8%	71%	2.3%	56%	2.9%	51%	3.4%	66%	1.2%
- Clear Cell carcinoma	55%	5.3%	56%	5.3%	55%	5.2%	58%	6.1%	57%	2.7%
- Adenosquamous carcinoma	77%	4.0%	66%	4.5%	70%	5.3%	70%	10.5%	72%	2.5%
Sarcomas	**47%**	**3.2%**	**53%**	**3.0%**	**46%**	**2.9**	**52%**	**3.4%**	**49%**	**1.5%**
- Leiomyosarcoma	42%	4.0%	40%	3.7%	36%	3.7%	44%	5.1%	40%	2.0%
- Endometrial stromal sarcoma high grade	60%	5.9%	71%	5.2%	44%	6.1%	30%	6.9%	53%	2.1%
- Endometrial stromal sarcoma low grade	*n*<10		*n*<10		89%	6.2%	95%	4.4%	92%	3.5%
- Adenosarcoma	*n*<10		97%	8.6%	63%	12.0%	72%	12.3%	78%	6.1%
Carcinosarcoma (Malignant Müllerian Mixed tumor)	**34%**	**3.5%**	**32%**	**3.3%**	**35%**	**3.2%**	**37%**	**3.3%**	**35%**	**1.7%**
Type unclear/ unspecified	**66%**	**7.4%**	**28%**	**7.4%**	**29%**	**8.1%**	***n*<10**		**43%**	**4.2%**

RS = Relative Survival, SE = Standard Error of relative survival; n<10 = Less than 10 patients are alive 5 years after diagnosis, therefore survival estimate is not presented
Source: NCR

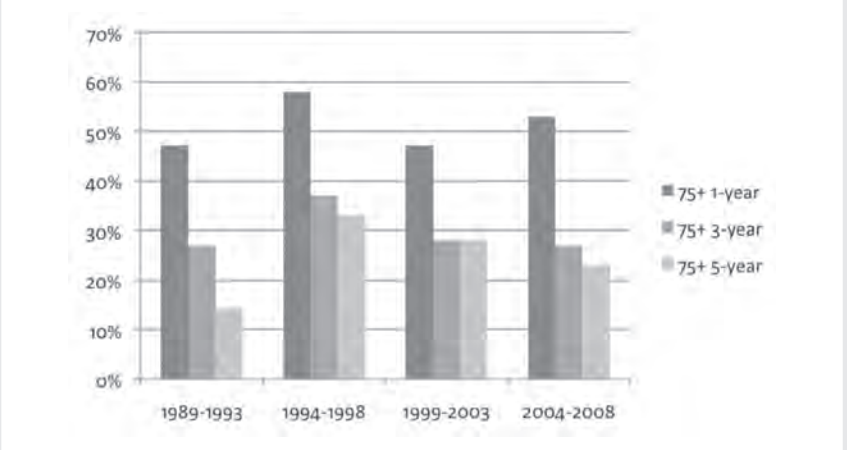

Figure 1 Relative survival (RS) carcinosarcomen 75+ years of age. One, -three and five-year survival. The Netherlands Cancer registry 1989-2008

The poor outcome for patients with UEEC was also described in a recent publication from the UK by Evans et al. [5]. In our study the differences in the outcome for patients with UEEC were due to changes in the classification of UEEC . In the past 20 years significant progress has been made in the practice of gynecologic pathology. Immunohistochemical and molecular biological advances contributed to more specific and precise definitions of tumor types, such as serous carcinomas and sarcomas, most likely reflected in shifts in incidence rates. The Dutch data show a decrease in incidence of serous carcinoma after the publication of Hendrickson in 1994[12], who modified the protocol for better differentiation between villoglandular endometrioid carcinomas and the diagnosis of uterine papillary serous adenocarcinoma. Consequently the five-year relative survival of patients diagnosed with serous adenocarcinoma after 1994 corresponds better with survival data described in other studies [14, 15, 15-21]. Another example of progress in histopathological diagnosis is the change in incidence and survival of ESS. Low grade ESS in general is an estrogen sensitive tumor, occurring at a younger age and with a favorable prognosis. High grade ESS is essentially an undifferentiated sarcoma, occurring in older women with an unfavorable prognosis[10]. After the publication by Amant [13] in 2004 the differentiation between low and high grade ESS became more accurate , which is reflected by the increased incidence of low grade ESS and the decrease in survival of the patients with high grade ESS. In summary, we can conclude that the major shifts in incidence and survival in patients with serous adenocarcinoma and sarcoma were due to changes in histopathological diagnosis.

Table 3.2 Five-year relative survival of patients aged 0-74 years with corpus uteri malignancy according to period of diagnosis and morphologic group. The Netherlands Cancer registry 1989-2008

Morphologic group	Period of diagnosis									
	1989-1993		1994-1998		1999-2003		2004-2008		Total period	
	RS	SE	RS	SE	RS	SE	RS	SE	RS	SE
Total	**81%**	**0.6%**	**82%**	**0.6%**	**83%**	**0.6%**	**84%**	**0.6%**	**83%**	**0.3%**
Common Epithelial Endometrial Carcinoma (CEEC)	**85%**	**0.7%**	**88%**	**0.6%**	**89%**	**0.6%**	**89%**	**0.6%**	**88%**	**0.3%**
- Endometrioid Adenocarcinoma (EAC)	85%	0.7%	88%	0.6%	89%	0.6%	89%	0.6%	88%	0.3%
- EAC with adenosquamous differentiation	88%	2.6%	92%	3.0%	87%	3.6%	91%	3.7%	89%	1.6%
- Mucinous adenocarcinoma	79%	6.5%	85%	5.1%	94%	5.9%	100%	3.0%	87%	3.0%
- Variants of EAC	*n*<10		*n*<10		98%	6.0%	82%	7.6%	87%	5.4%
Uncommon epithelial Endometrial Carcinoma (UEEC)	**78%**	**1.5%**	**71%**	**2.0%**	**63%**	**2.4%**	**60%**	**3.0%**	**71%**	**1.0%**
- Serous carcinoma	81%	1.7%	72%	2.4%	62%	3.2%	56%	3.8%	72%	1.2%
- Clear Cell carcinoma	58%	5.8%	69%	6.0%	59%	5.8%	67%	7.0%	64%	3.0%
- Adenosquamous carcinoma	75%	4.0%	73%	4.5%	70%	5.7%	70%	10.4%	73%	2.5%
Sarcomas	**50%**	**3.4%**	**56%**	**3.1%**	**48%**	**3.0%**	**54%**	**3.6%**	**52%**	**1.6%**
- Leiomyosarcoma	45%	4.2%	44%	3.9%	38%	3.9%	43%	5.3%	42%	2.1%
- Endometrial stromal sarcoma high grade	62%	6.1%	73%	5.1%	49%	6.5%	*n*<10		58%	3.2%
- Endometrial stromal sarcoma low grade	*n*<10		*n*<10		89%	5.8%	94%	4.1%	92%	3.2%
- Adenosarcoma	*n*<10		90%	9.9%	65%	12.5%	82%	12.7%	82%	6.1%
Carcinosarcoma (Malignant Müllerian Mixed tumor)	**42%**	**4.2%**	**32%**	**3.8%**	**40%**	**4.0%**	**44%**	**4.0%**	**40%**	**2.0%**

RS = Relative Survival, SE = Standard Error of relative survival,
n<10 = Less than 10 patients are alive 5 years after diagnosis, therefore survival estimate is not presented
Source: NCR

Table 3.3 Five-year relative survival of patients aged 75+ years with corpus uteri malignancy according to period of diagnosis and morphologic group. The Netherlands Cancer registry 1989-2008

Morphologic group	Period of diagnosis									
	1989-1993		1994-1998		1999-2003		2004-2008		Total period	
	RS	SE	RS	SE	RS	SE	RS	SE	RS	SE
Total	**65%**	**1.8%**	**65%**	**1.7%**	**68%**	**1.6%**	**69%**	**1.9%**	**66%**	**0.9%**
Common Epithelial Endometrial Carcinoma (CEEC)	**73%**	**2.2%**	**71%**	**2.0%**	**75%**	**1.8%**	**77%**	**2.2%**	**74%**	**1.0%**
- Endometrioid Adenocarcinoma (EAC)	72%	2.3%	70%	2.0%	75%	1.9%	77%	2.2%	74%	1.0%
- EAC with adenosquamous differentiation	75%	9.4%	80%	11.7%	72%	12.8%	.	12.8%	78%	5.9%
- Mucinous adenocarcinoma	72%	15.6%	99%	13.6%	*n*<10		*n*<10		86%	8.5%
- Variants of EAC	*n*<10		*n*<10		*n*<10		*n*<10		*n*<10	
Uncommon epithelial Endometrial Carcinoma (UEEC)	**52%**	**4.0%**	**55%**	**4.2%**	**47%**	**4.7%**	**40%**	**5.8%**	**49%**	**2.2%**
- Serous carcinoma	48%	4.4%	66%	5.2%	42%	5.8%	39%	7.4%	51%	2.7%
- Clear Cell carcinoma	47%	11.4%	36%	9.0%	47%	10.2%	45%	10.9%	43%	5.1%
- Adenosquamous carcinoma	87%	13.1%	*n*<10		70%	13.0%	*n*<10		65%	7.8%
Sarcomas	**29%**	**9.0%**	**29%**	**9.1%**	**33%**	**8.5%**	***n*<10**		**31%**	**4.6%**
Carcinosarcoma (Malignant Müllerian Mixed tumor)	**14%**	**5.5%**	**33%**	**7.1%**	**28%**	**5.6%**	**23%**	**5.5%**	**25%**	**3.0%**

RS = Relative Survival, SE = Standard Error of relative survival,
n<10 = Less than 10 patients are alive 5 years after diagnosis, therefore survival estimate is not presented
Source: NCR

In our study a modest increase (from 5.1 to 6.9) was seen in the age-standardized incidence of carcinosarcomas, previously known as malignant müllerian mixed tumor. The origin of these malignancies has long been debated, due to the uncertain relationship between epithelial and mesenchymal malignant cells [22, 23], prompting us to perform a separate analysis of this tumor type. Originally, it was thought that malignant mixed müllerian tumor represented a sarcoma, but since 1997 these malignancies are considered to be metaplastic carcinomas, the behavior of which is rather determined mainly by the

epithelial element[24]. The incidence is higher among patients older than 75 years of age[24]. In the literature the relationship between tamoxifen therapy for breast cancer patients and an increased risk of endometrial carcinosarcomas is suggested. Two studies conducted between 1980-2001 (Alert [25]and Tamarisk[26]) found a relationship between tamoxifen and a higher risk of carcinosarcomas. It is striking that a high percentage of the patients in the tamoxifen group were older (older than 70 years). This is due to the fact that tamoxifen in the eighties and the nineties of the last century was prescribed mainly to postmenopausal breast cancer patients. It is possible that the higher incidence of carcinosarcomas found in the tamoxifen group is influenced by the higher incidence of carcinosarcomas in older patients (median age 71) [24]. It should be taken into account that after 2000[27] prescription of tamoxifen changed and included premenopausal patients; moreover the publication of Herk et al. [28] showed an independent relationship between older age and discontinuation of tamoxifen. Another publication [29] on the tumor genomic profile of endometrial carcinoma could not distinguish tamoxifen users from nonusers on the basis of their tumor genomic profile. In summary we can conclude that the relationship between tamoxifen use and a higher incidence of less favorable histology of endometrial carcinoma is still a matter of debate and less clear than formerly expected and the modest increase in incidence of carcinosarcomas in this large population based study is less than was expected on the basis of the earlier mentioned studies[30].
Our findings show that accurate histopathological diagnosis of rare tumors by pathologists and clinicians is of vital importance because of the clinical, prognostic and therapeutic implications. The increasing complexity of histopathology and immune-histochemistry should stimulate the general pathologist to consult (inter)national expert groups in order to obtain the best possible diagnosis for the treatment protocol. Potential limitations of this study are incomplete data entries in some cases, heterogeneity of pathological assessments and a lack of central pathology review, but as with other population-based series, we were unable to carry out a central pathology review of all 7,494 patients who had an uncommon pathology. Nevertheless, our study reveals a clear improvement in tumor diagnosis and classification in The Netherlands between1989 and 2008.

Conclusion

The decrease in UEEC tumors may be largely due to the exclusion of villoglandular tumors, a variant of EAC. The main changes in incidence and survival can most likely be attributed to improved histopathological diagnosis and classification. Unfortunately, relative survival for patients with UEEC, sarcomas and carcinosarcomas did not improve over the study period, indicating a need for more research on treatment strategies for this group of patients. Furthermore there is a need for more research into molecular biology and carcinogenesis of these high grade and rare tumors for better understanding.

Reference List

[1] Ferlay J., Shin H.R., Bray F., Forman D., Mathers C., Parkin D.M. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* ;**127**:2893-917;2010

[2] CBS statline. statline.cbs.nl . 2011. 1-1-2011. Ref Type: Internet Communication

[3] De A.R., Francisci S., Baili P., Marchesi F., Roazzi P., Belot A. et al. The EUROCARE-4 database on cancer survival in Europe: data standardisation, quality control and methods of statistical analysis. *Eur J Cancer* ;**45**:909-30;2009

[4] Renehan A.G., Tyson M., Egger M., Heller R.F., Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* ;**371**:569-78;2008

[5] Evans T., Sany O., Pearmain P., Ganesan R., Blann A., Sundar S. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. *Br J Cancer* ;**104**:1505-10;2011

[6] Tavassoli F.A., Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs, WHO. Tavassoli F.A., Devilee P, editors. 1-1-2003. Lyon, IARCPress. 1-1-2003. Ref Type: Serial (Book,Monograph)

[7] Hermanek P., Hutter R., Sobin L., Wagner G., Wittekind C. TNM atlas. fouth. 1997. Berlin, Springer-Verlag. Ref Type: Serial (Book,Monograph)

[8] Schouten L.J., Hoppener P., van den Brandt P.A., Knottnerus J.A., Jager J.J. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* ;**22**:369-76;1993

[9] Hermanek P., Hutter R., Sobin L., Wagner G., Wittekind C. TNM atlas. fouth. 1997. Berlin, Springer-Verlag. Ref Type: Serial (Book,Monograph)

[10] Robert J.Kurman. Blaustein's Pathology of the Female Genital Tract. *Fifth edition* ;2002

[11] Dickman P.W., Sloggett A., Hills M., Hakulinen T. Regression models for relative survival. *Stat Med* ;**23**:51-64;2004

[12] Hendrickson M.R., Longacre T.A., Kempson R.L. Uterine papillary serous carcinoma revisited. *Gynecol Oncol*; **54**:261-3;1994

[13] Amant F., Vergote I., Moerman P. The classification of a uterine sarcoma as 'high-grade endometrial stromal sarcoma' should be abandoned. *Gynecol Oncol* ;**95**:412-3;2004

[14] Kato D.T., Ferry J.A., Goodman A., Sullinger J., Scully R.E., Goff B.A. et al. Uterine papillary serous carcinoma (UPSC): a clinicopathologic study of 30 cases. *Gynecol Oncol* ;**59**:384-9;1995

[15] Goff B.A., Kato D., Schmidt R.A., Ek M., Ferry J.A., Muntz H.G. et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol* ;**54**:264-8;1994

[16] Fader A.N., Drake R.D., O'Malley D.M., Gibbons H.E., Huh W.K., Havrilesky L.J. et al. Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. *Cancer* ;**115**:2119-27;2009

[17] Fader A.N., Starks D., Gehrig P.A., Secord A.A., Frasure H.E., O'Malley D.M. et al. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). *Gynecol Oncol* ;**115**:244-8;2009

[18] Havrilesky L.J., Secord A.A., Bae-Jump V., Ayeni T., Calingaert B., Clarke-Pearson D.L. et al. Outcomes in surgical stage I uterine papillary serous carcinoma. *Gynecol Oncol* ;**105**:677-82;2007

[19] Goff B.A., Kato D., Schmidt R.A., Ek M., Ferry J.A., Muntz H.G. et al. Uterine papillary serous carcinoma: patterns of metastatic spread. *Gynecol Oncol* ;**54**:264-8;1994

[20] Boruta D.M., Gehrig P.A., Fader A.N., Olawaiye A.B. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. *Gynecol Oncol* ;**115**:142-53;2009

[21] Clement P.B., Young R.H. Non-endometrioid carcinomas of the uterine corpus: a review of their pathology with emphasis on recent advances and problematic aspects. *Adv Anat Pathol* ;**11**:117-42;2004

[22] Bitterman P., Chun B., Kurman R.J. The significance of epithelial differentiation in mixed mesodermal tumors of the uterus. A clinicopathologic and immunohistochemical study. *Am J Surg Pathol* ;**14**:317-28;1990

[23] Abeln E.C., Smit V.T., Wessels J.W., de Leeuw W.J., Cornelisse C.J., Fleuren G.J. Molecular genetic evidence for the conversion hypothesis of the origin of malignant mixed mullerian tumours. *J Pathol* ;**183**:424-31;1997

[24] D'Angelo E., Prat J. Uterine sarcomas: a review. *Gynecol Oncol* ;**116**:131-9;2010

[25] Bergman L., Beelen M.L., Gallee M.P., Hollema H., Benraadt J., van Leeuwen F.E. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* ;**356**:881-7;2000

[26] Hoogendoorn W.E., Hollema H., van Boven H.H., Bergman E., de Leeuw-Mantel G., Platteel I. et al. Prognosis of uterine corpus cancer after tamoxifen treatment for breast cancer. *Breast Cancer Res Treat* ;**112**:99-108;2008

[27] Sukel M.P., van de Poll-Franse LV, Nieuwenhuijzen G.A., Vreugdenhil G., Herings R.M., Coebergh J.W. et al. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands. *Eur J Cancer* ;**44**:1846-54;2008

[28] van Herk-Sukel M.P., van de Poll-Franse LV, Voogd A.C., Nieuwenhuijzen G.A., Coebergh J.W., Herings R.M. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis. *Breast Cancer Res Treat* ;**122**:843-51;2010

[29] Fles R., Hoogendoorn W.E., Platteel I., Scheerman C.E., de Leeuw-Mantel G., Mourits M.J. et al. Genomic profile of endometrial tumors depends on morphological subtype, not on tamoxifen exposure. *Genes Chromosomes Cancer* ;**49**:699-710;2010

[30] Bergman L., Beelen M.L., Gallee M.P., Hollema H., Benraadt J., van Leeuwen F.E. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* ;**356**:881-7;2000

3

Role of co-morbidity and Quality of care

3.1. **Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995–2008**

3.2. **Effect of diabetes on endometrial cancer recurrence and survival**

3.1

Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008

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Abstract

Background

Endometrial cancer (EC) occurs more frequently among women over 60 years old, who often also suffer from co-morbidity. Since treatment guidelines are derived from clinical trials that usually exclude such patients, nevertheless these guidelines are also applied for older EC patients. We assessed the independent influence of age and co-morbidity on treatment modalities and survival of patients with stage I EC in everyday clinical practice, thereby also examining the implementation of Dutch guidelines on treatment, since 2000.

Methods

All 2099 stage I EC patients diagnosed between 1995 and 2008 in the southern The Netherlands were registered in the ECR (Eindhoven Cancer Registry) were included for analysis of the influence of age and co-morbidity on treatment and survival. For co-morbidity we used a modified version of the Charlson's list, uniquely recorded in the ECR since 1993. A subgroup analysis was performed of patients who should have received adjuvant radiotherapy based on the risk factors advised in the Dutch guidelines of 2000. We considered five periods (1995-97; 1989-2000; 2001-03; 2004-06; 2007-08)

Results

Having two or more co-morbid conditions resulted in a significant reduction of receiving adjuvant radiotherapy (Odds Ratio : 0.6, 95% Confidence Interval (95% CI): 0.3-1.0)) but receiving adjuvant radiotherapy did not appear to improve survival. After adjustment for age, tumour stage, tumour grade, period of diagnosis and treatment, co-morbidity increased the risk of death, especially diabetes (Hazard Ratio (HR) for mortality: 2.9 ,95% CI: 2.2-4.0), a previous cancer (HR: 2.6, 95%CI: 1.9-3.7) and cardiovascular disease (HR: 2.3, 95%CI: 1.7-3.2). The combination of two or more co-morbid conditions resulted in a HR of 3.0 (95%CI: 2.2-3.9).

Conclusion

Co-morbidity decreased the likelihood of receiving adjuvant radiotherapy in patients with stage I EC qualifying to undergo this according to the Dutch guidelines of 2000. Whereas adjuvant radiotherapy did not seem to affect survival in those patients, co-morbidity significantly did.

Background

Endometrial Cancer (EC) is the most common gynaecological cancer in industrialized countries. In The Netherlands it affects approximately 1700 women per year of whom 300 to 350 die each year.[1,2] Seventy to eighty percent of all cases of EC are diagnosed at an early stage (International Federation of Gynaecology and Obstetrics [FIGO] 1988 stage I) and generally have a good prognosis.[3] The tumour develops predominantly in women aged 60 years or older. In The Netherlands, as well as in the rest of the industrialized world, the incidence of EC has been increasing slightly. [2,4-8] This is due to increased life expectancy and changes in lifestyle factors, leading for example to obesity.[5,6] EC often develops in older women who, because of their age, are likely to have other chronic disabling conditions (co-morbidity).[7] Some of these conditions, such as diabetes, hypertension and obesity, are in themselves associated with an increased risk of EC. [4-8] For patients with serious co-morbidity, a physician might decide to alter standard oncological treatment due to an increased risk of side effects or limited life expectancy.

Total abdominal hysterectomy with bilateral resection of the ovaries is the cornerstone of treatment for stage I EC. Up to the year 2000 adjuvant pelvic radiotherapy was advised for almost all stage I EC patients, except those with low-grade tumours and superficial invasion. Bases on the results of the Portec trial, [9] the guidelines were changed in 2000 into consideration of adjuvant radiotherapy only in the presence of two or thereof the risk factors (> 50% myometrial invasion, grade 3 histological type, age ≥60 years). Adjuvant radiotherapy in this situation reduces the likelihood of loco regional recurrence by 3-10 %, but has no impact on overall survival.[9,10-12]

This population-based study, carried out in a region with medium to large general hospitals only and two large radiation therapy centres, investigated the effect of co-morbidity uniquely recorded in the ECR, on the choice of treatment and survival rates in patients with stage 1 EC.

Methods

Data collection

All newly diagnosed patients (*n*=2099) with stage I EC diagnosed between 1 January 1995 and 31 December 2008 were selected from the ECR (Eindhoven Cancer Registry), that registers data of all newly diagnosed patients with cancer occurring in 2.4 million inhabitants in the southern The Netherlands. After notification from the pathological laboratories or the medical registration offices, trained registration clerks collected data from the medical records on diagnosis, tumour stage and treatment and since 1983 also serious co-morbidity with prognostic impact. The medical record is generally regarded as the most complete source of information on the patients past and current health status.[13]

The list of co-morbidity is a modified version of the Charlson co-morbidity index (table1). Co-morbidity was defined as diseases that were present at the time of the cancer diagnosis.[14] In case of two different cardiovascular conditions each of them was registered. The completeness and accuracy of the co-morbidity data in the ECR were validated between 2001-2003[14] and only a slight under registration occurred (especially of cardio-vascular conditions). Tumour stage was defined according to the FIGO staging system, based on postoperative information. FIGO stage I EC was divided into stage Ia (no myometrial invasion), Ib (less than 50% myometrial invasion) and Ic (more than 50% myometrial invasion). In The Netherlands, guidelines for primary treatment and adjuvant treatment as implemented in 2000, were based on the results of the randomized Portec I trial on adjuvant radiotherapy (1990-1997).[9]

Furthermore, five hospitals in the ECR region participated in a separate study routine performance of pelvic lymph adenectomy for 237 patients with stage I EC from 1995 to 2004 (13% of the total population of this study). If the pelvic lymph nodes were negative, no radiotherapy was given, regardless of the presence of the aforementioned risk factors.[15] This resulted in a total of 71 (4%) patients who were not treated according to the Dutch guidelines of 2000.[16] We considered five periods (1995-97; 1998-2000; 2001-03; 2004-06; 2007-08), to analyze the influence on referral for adjuvant radiotherapy with these two studies in mind.

Vital status was available up to January 1 2009. In addition to results from passive follow-up data of the hospitals, information was also obtained from the Municipality Administration Database, in which deceased and emigrated persons in The Netherlands are registered via the civil municipal registries.

Statistical analysis

The prevalence of co-morbidity was analyzed according to age (under 60 versus 60 and older).

For a subgroup analysis, a selection was made of patients who should have received adjuvant radiotherapy in accordance with the risk factors as advised in the current Dutch guidelines.[16] This selection was made for patients treated between 2000 and 2008 and led to 444 patients who should have received adjuvant radiotherapy. Prior to 2000, either gynaecologists participated in the Portec trial, or referred patients on their own insight, resulting in a heterogeneous approach, therefore patients diagnosed before 2000 were excluded from this subgroup analysis. After exclusion of patients (n=57) with unknown grade, unknown co-morbidity and without a subdivision of stage I, 387 patients out of 444 remained for multivariate analysis. Logistic regression was used to investigate which factors influenced the likelihood of receiving adjuvant radiotherapy. First, the effect of the number of co-morbid conditions (0, 1, 2+) was evaluated. Thereafter, the effects of the most common types of co-morbidity (diabetes, cardiovascular disease, hypertension and previous malignancy) were also evaluated in separate models, each adjusted for the same

Table 1 Classification of co-morbidity, as recorded in the Eindhoven Cancer Registry

Previous malignancies (except basal cell skin carcinoma and cervical carcinoma in situ)
Chronic obstructive pulmonary diseases
Cardiovascular diseases Myocardial infarction Heart failure Angina pectoris Cardiomyopathy Valve prothesis (aorta or mitralis) Intermittent claudication Abdominal aneurysm Thromboembolic events
Cerebrovascular diseases Cerebrovascular accident Hemiplegia
Hypertension
Liver disease (cirrhosis, hepatitis)
Diabetes mellitus
Other Digestive tract diseases (Ulcerative disease, Chronic inflammatory diseases) Urinary tract diseases Connective tissue diseases Dementia Chronic infections

covariates as the model for the number of co-morbid conditions (age, FIGO stage, grade and period of diagnosis). Crude 3-year and 5-year univariate survival rates were computed. Survival time was defined as the time from diagnosis to death. Patients who were still alive at the end of the study were censored on January 1 2009. The prognostic effects of age and number of co-morbid conditions on survival were estimated in a multivariate Cox regression model adjusted for stage, grade, period of diagnosis and radiotherapy. Comparable to logistic regression analyses, the prognostic effects on survival of the most common types of co-morbidity (diabetes, cardiovascular disease, hypertension and previous malignancy) were also evaluated in separate models, each adjusted for the same covariates as the model for the number of co-morbid conditions.

Results

The 2099 patients newly diagnosed with stage I EC during 1995 and 2008 had a mean age of 64 (range 28-91) and 66% were 60 years or older at the time of diagnosis. In figure 1, the treatment modalities are shown according to age and co-morbidity. In patients aged 60 years and older, the percentage receiving adjuvant radiotherapy were more than threefold higher (26-31%) as compared to those younger than 60 years of age (7-9%). In 98% of patients, hysterectomy was performed. Co-morbidity was present in 59 % of patients receiving a hysterectomy. So co-morbidity did not affect the choice for hysterectomy. Less than 1% received only radiotherapy. Respectively ten patients (1.2%) in the group younger than 60 years of age and twelve (1.0%) patients of 60 years and older did not receive either hysterectomy or radiotherapy. Some of them received a not specified type of surgery. Information about the implementation of the Dutch guidelines (published in 2000)[13] is

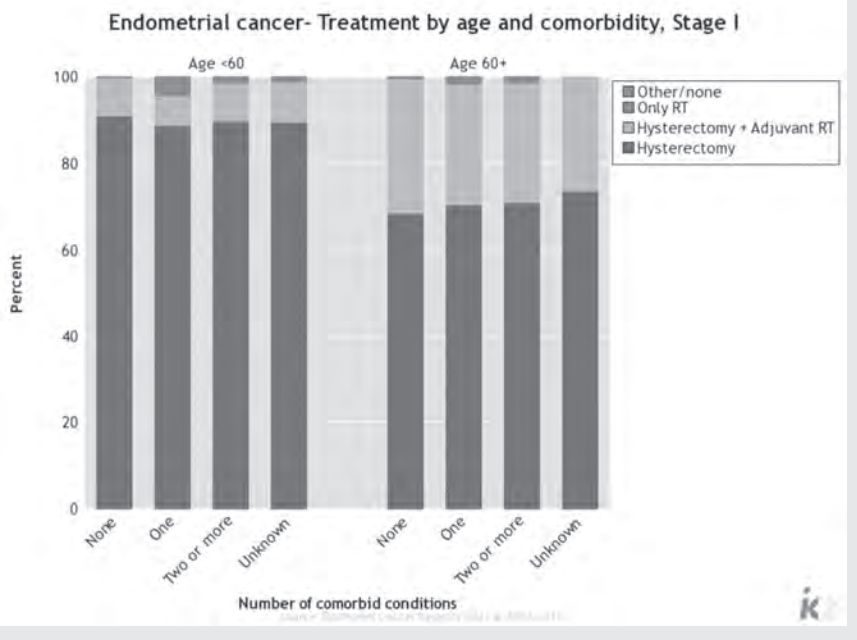

Figure 1 Treatment of stage I endometrial cancer according to age and number of co-morbid conditions in a population of n=2099 unselected patients in the Eindhoven Cancer Registry (ECR) region. Period of diagnosis 1995-2008

Hysterectomy = hysterectomy and bilateral oophorectomy
RT= radiotherapy

shown in table 2. The two out of three risk factors rule for receiving adjuvant radiotherapy (age ≥60 years, more than 50% invasion of the myometrium, and grade 3 disease) was retrospectively used for the total population of 2099 patients (table 2). The percentage of patients receiving adjuvant radiotherapy, although this was not recommended according to the guidelines, was 18 % (underlined numbers in table 2) in the first period from 1995 to 1997 and decreased to 2-5% in the following periods. The group who underwent a hysterectomy without adjuvant radiotherapy as recommended increased from 79% in the

Table 2 Treatment recommendations according to the Dutch guidelines (2000) and actual treatment delivery during 1995-1997; 1998-2000; 2001-2003; 2004-2006; 2007-2008.

	Treatment given				
	N *(%)*	N*(%)*	n	N (%)	total
Treatment according to guidelines	Hysterectomy	Hysterectomy and Adj RT[1]	RT[2]	No Hysterectomy and no Adj RT[1]	
1995-1997					
Hysterectomy	**199 *(79%)***	46 *(18%)*	2 (1%)	4 *(2%)*	251
Hysterectomy and Adj RT[1]	54 *(45%)*	64 *(54%)*	1 (1%)	0	119
1998-2000					
Hysterectomy	**275 *(94%)***	15 *(5%)*	0	2 *(1%)*	292
Hysterectomy and Adj RT[1]	62 *(47%)*	69 *(53%)*	0	0	131
2001-2003					
Hysterectomy	**293 *(95%)***	11 *(4%)*	2	3 *(1%)*	309
Hysterectomy and Adj RT[1]	59 *(46%)*	67 *(53%)*	0	1 *(1%)*	127
2004-2006					
Hysterectomy	**331 *(93%)***	12 *(2%)*	0	11 *(5%)*	354
Hysterectomy and Adj RT[1]	64 *(39%)*	100 *(60%)*	0	2 *(1%)*	166
2007-2008					
Hysterectomy	**229 *(95%)***	12 *(5%)*	0	0	241
Hysterectomy and Adj RT[1]	48 *(44%)*	59 *(54%)*	2 (1%)	0	109
1995-2008					
Hysterectomy	**1327 *(92%)***	98 *(7%)*	4	20 *(1%)*	1447
Hysterectomy and Adj RT[1]	287 *(44%)*	359 *(55%)*	1	5 (1%)	652
	1614 *(77%)*	457 *(22%)*	5	23 *(1%)*	2099
2000-2008[3]					
Hysterectomy	942 *(94%)*	49 *(5%)*	2	10 *(1%)*	1003
Hysterectomy and Adj RT[1]	195 *(44%)*	244 *(55%)*	2	3 *(1%)*	444

[1] Adj RT=adjuvant radiotherapy
[2] RT=radiotherapy
[3] for deduction of numbers for subgroup analysis in table 3

first period from 1995 to 1997, to 93-95% in the following periods (bold numbers in table 2). The percentage of patients who should have received adjuvant radiotherapy according to the guidelines but who were not referred varied between 39-47%.

Table 3 shows the results of a multivariate analysis of determinants of referral in the 387 patients who should have received adjuvant radiotherapy according to the guidelines[13]. Patients with Stage Ic had a significant influence on whether patients received radiotherapy (Odds Ratio (OR) was 4.7 (95% CI 1.4 -16)). Patients with two or more co-morbid conditions received significantly less adjuvant radiotherapy with an OR of 0.6 (95% CI: 0.3-0.96).

For univariate and multivariate survival analyses, patients were excluded because of missing information on co-morbidity (n=207), grade (n=92) and stage (n=30) leaving 1770 patients for further analysis.

In table 4, crude 3 and 5-year univariate survival and HR (Hazard Ratio) for mortality are shown according to age, stage, grade, number of concomitant conditions, type of co-morbidity and also taking primary treatment into account.

Five-year survival for patients aged 60 years and older was 82%, a drop of 11% compared to 93% 5-year survival for those younger than 60 years of age. For patients with two or

Table 3 Multivariate regression analysis of odds of receiving adjuvant radiotherapy (OR) in a subgroup of 387[1] patients diagnosed during 2000-2008 based on two out of three rule of the Dutch treatment guidelines.

		n	%	OR	95% CI#
Age	< 60 years	13	3.4	1.0	-
	≥ 60 years	374	97	1.6	0.5-5.6
FIGO	IA	18	4.6		
	IB	36	9.3	1.8	0.5-6.7
	IC	**333**	**86**	**4.7**	**1.4-16**
Period of diagnosis	2000-2002	100	26	1.0	-
	2003-2005	131	34	1.0	0.6-1.7
	2006-2008	156	40	1.5	0.9-2.6
No. of co-morbidities	0	112	29	1.0	-
	1	148	38	0.8	0.5-1.3
	2+	**127**	**33**	**0.6**	**0.3-0.96**
Co-morbidity	Cardiovascular	95	25	0.8	0.4-1.3
	Diabetes	85	27	0.8	0.5-1.3
	Hypertension	166	43	0.9	0.6-1.3
	Previous cancer	56	14	0.7	0.4-1.2

95% Confidence Interval

[1] 2000-2008 n=444 (table2) minus 57 patients with incomplete data: 387 patients were left for multivariate regression analysis

Table 4 Crude univariate three and five-year survival and multivariable Hazard ratios (HR) for endometrial cancer in the south of The Netherlands 1995-2008 (n=1770)

		n	(%)	3-year survival (%)	5-year survival (%)	HR [3]	[4]95%CI
Age	<60 years	579	33%	96%	93%	Ref	
	≥60 years	1191	67%	88%	82%	3.0	2.1-4.2
FIGO[1]	IA	274	15%	91%	87%	Ref	
	IB	902	51%	93%	89%	1.0	0.7-1.4
	IC	594	34%	87%	80%	1.4	1.0-2.1
Grade	Low/intermediate	1531	87%	93%	89%	Ref	
	High	239	14%	79%	67%	2.5	1.9-3.2
Period of diagnosis	1995-1997	332	19%	91%	85%	Ref	
	1998-2000	370	21%	90%	85%	0.8	0.6-1.0
	2001-2003	341	19%	90%	87%	0.8	0.5-1.1
	2004-2006	418	24%	93%	-	0.7	0.5-1.1
	2007-2008	309	17%	-	-	0.8	0.4-1.7
Number of co-morbidity	0	721	41%	95%	91%	Ref	
	1	605	34%	92%	88%	1.4	1.0-1.9
	2+	444	25%	82%	74%	3.0	2.2-3.9*
Type co-morbidity[2]	Cardiovascular	281	16%	83%	76%	2.3	1.7-3.2
	Diabetes	304	17%	85%	74%	2.9	2.2-4.0
	Hypertension	596	34%	88%	82%	1.8	1.4-2.4
	Previous cancer	232	13%	83%	75%	2.6	1.9-3.7
Primary treatment	Hysterectomy	1366	77%	92%	88%	Ref	
	Hysterectomy + ART[5]	404	23%	87%	79%	1.0	0.7-1.3

[1]FIGO= International Federation of Gynecology and Obstetrics staging system 1988; [2]Reference category is no co-morbidity; [3]HR=multivariate hazard ratio for death; [4] CI=Confidence Interval; [5]ART=adjuvant radiotherapy;* Statistically significant

more co-morbid conditions the five-year survival was 73% versus 91% for those without co-morbidity. For patients with diabetes five year survival was 74% for patients with cardiovascular disease this was 76% and for patients with a previous malignancy this was 75 %. Period of diagnosis had no independent influence on survival. The multivariate HR for mortality was 3.0 (95%CI: 2.1-4.2) for patients aged 60 years and older compared to younger patients. The HR for mortality for patients with diabetes versus no co-morbidity was 2.9 (95% CI: 2.2-4.0), 2.6 (95% CI 1.9-3.7) for previous malignancy versus no co-morbidity and 2.3 (95% CI: 1.7-3.2) for cardiovascular disease versus no co-morbidity. The multivariable HR for mortality for adjuvant radiotherapy was 1.0 (95% CI:0.7-1.3).

Discussion

Co-morbidity had no influence on the resection rate in this population of 2099 patients diagnosed with stage I EC between 1995 and 2008; 98-99% of the patients underwent hysterectomy. This was also seen in other tumours were there are no alternatives for surgery, for example in patients with colorectal cancer.[17,18] In contrast, we found that patients with two or more co-morbid conditions were less likely to receive adjuvant radiotherapy, even after implementation of the Dutch guidelines in 2000[13]. Survival was clearly poorer for patients with co-morbidity compared to patients without co-morbidity, especially for those with diabetes, cardiovascular disease and previous malignancy.
In 1999, just before the implementation of the new Dutch guidelines, a decrease in the proportion of patients receiving adjuvant radiotherapy already occurred (table 2). This can be explained by the fact that in 1999, most of the gynaecological oncologists and radiotherapists had already been informed about the results of the Portec I trial,[9] which only recommended referral for adjuvant radiotherapy when patients had two out of the three risk factors (age ≥60 years, more than 50% invasion of the myometrium, and grade 3 disease). On the other hand, the percentage of patients indicated to receive radiotherapy due to the risk factors listed above and in whom adjuvant radiotherapy was not performed, remained considerable (between 39% and 47%). This percentage was neither influenced by the implementation of the guidelines nor by a study performed in five of the hospitals in the ECR region.[12] This study on lymph-adenectomy in stage I EC was conducted from 1998 to 2004. In this study only 71 patients (or 4%) did not receive adjuvant radiotherapy when lymph nodes were negative, although two of the risk factors listed above were positive.

In the multivariate analysis on a subgroup of 387 patients who had two out of the above mentioned risk factors and should have received adjuvant radiotherapy according to the Dutch guidelines of 2000,[13] a significant reduction in receiving adjuvant radiotherapy was found, when two or more co-morbid conditions were present. Several studies have shown

that patients with co-morbidity are less likely to be treated according to guidelines than patients without co-morbidity.[2,4-8] A publication on treatment guidelines for breast cancer has shown that co-morbidity was the most frequently stated reason for deviating from treatment guidelines (11 out of 18 motivated deviations).[19,20] Serious co-morbidity can be a legitimate reason for deviating from treatment guidelines if the life expectancy of a patient is significantly reduced by it. Besides that, 31% of treatment omissions were due to patient preference. The Portec 1 trial[9] has shown that protocol violations occurred in the radiotherapy group. In twelve out of 23 patients radiotherapy was refused by patients. Reasons for not recommending adjuvant radiotherapy for gynaecologists were: old age, co-morbidity or negative judgment of its benefit. The value of postoperative radiotherapy is controversial, although pelvic radiotherapy reduces vaginal and pelvic relapse, distant metastases still occur in this group and no survival benefit has been confirmed.[9,10-12] When a patient either or not with serious co-morbidity, is frail or older than 80 years of age, thorough follow up is a reasonable alternative, because high salvage rates with radiotherapy are reported among patients with local recurrence.[9,10-12]

As was expected, age and co-morbidity turned out to be highly predictive factors for survival after adjustment for tumour stage, tumour grade, period of diagnosis and treatment. However the decrease in survival of 15- 17% in patients with cardiovascular disease, previous malignancy and diabetes as compared to patients without co-morbidity are impressive. Clinical and biological interaction between diabetes and endometrial cancer is explained partly by the presence of higher levels of insulin in Type 2 diabetes mellitus, which results in higher levels of bio-available estrogens, partly due to the enhancing effect of insulin–like growth factors resulting in endometrial mitogenesis. [4-8,21,22] Cardiovascular disease, hypertension and diabetes are related to obesity. In obese patients the peripheral conversion of androstenedione to estrone by adipocytes leads to a chronic low-level increase in estrogen exposure leading to an increased risk of EC.[5] Because no information on the disease-specific cause of death was available in our study, we cannot answer the question whether co-morbidity results in earlier death or whether it affects the course of EC, for example, by earlier recurrence or metastasis. The different pathways to a diabetes-related mortality risk are not yet known. Patients have a poorer prognosis in case of a previous cancer as co-morbid condition. This is possibly due to therapeutic influence like tamoxifen use in case of previous breast cancer or radiation therapy in case of previous cervical cancer or colorectal cancer.[26,27] Tamoxifen and previous radiation therapy has been associated with a higher proportion of unfavourable uterine tumour subtypes with worse survival.[23,24] Furthermore a lower social economic status (SES) is related to an increased prevalence of co-morbidity, with more frequent diabetes, obesity and increased risk of breast and endometrial cancer and a poorer overall prognosis.[25] Obesity may affect the selection of treatment modalities for patients with endometrial cancer, although several studies suggest that comprehensive surgical staging for endometrial carcinoma can be performed in obese patients with similar operative

morbidity as in patients of ideal body weight. In this population based study we found that surgery was equally performed in patients with co-morbidity and in patients without co-morbidity.[26,27] Poorer survival in patients with previous cancer can also be related to prognosis of the first malignancy.

Although this population-based study had the advantage of being able to avoid a selection bias, detailed information on performance status of the patient and treatment-related effects other than mortality such as recurrence and long term complications were not available. These and other factors, such as cognitive disorders and frailty, also play a role in how patients are selected for effective and safe treatment.[18] Also information about staging procedures was not available. Moreover, the cause of death was unknown. We could therefore not evaluate whether patients with co-morbidity had a higher risk of dying as a result of endometrial cancer. To understand referral patterns we need alternative strategies, because of the large individual variations in physical and mental conditions and personal preferences of patients and physicians prevailing influence on decision-making process.

In conclusion, co-morbidity did not affect the proportion of patients with stage I endometrial cancer undergoing hysterectomy but had a strong association with not receiving adjuvant radiotherapy. The receipt of adjuvant radiotherapy did not appear to affect survival, which was clearly poorer in patients with co-morbidity, especially those with diabetes, previous malignancy and cardiovascular disease. The limited advantages of better loco-regional control of adjuvant radiotherapy should be weighted against the real dangers of co-morbidity and these patients might need a more explicit multidisciplinary surveillance in order to improve survival rates and quality of life by avoiding complications and promoting specific rehabilitation by preventing overweight, obesity and type II diabetes.

References

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*;**46**:765-81.
2. Comprehensive Cancer Centers and imageviewer. http://www.ikcnet.nl/page.php?id=109. retrieved 6-2-2007.
3. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet* 2005;**366**:491-505.
4. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *British journal of cancer* 2008;**98**:1582-5.
5. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. *Gynecologic oncology* 2009;**114**:121-7.
6. Hjartaker A, Langseth H, Weiderpass E. Obesity and diabetes epidemics: cancer repercussions. *Advances in experimental medicine and biology* 2008;**630**:72-93.
7. Saltzman BS, Doherty JA, Hill DA, et al. Diabetes and endometrial cancer: an evaluation of the modifying effects of other known risk factors. *American journal of epidemiology* 2008;**167**:607-14.
8. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). *Cancer Causes Control* 2000;**11**:185-92.
9. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;**355**:1404-11.
10. H M Keys, J A Roberts V L Brunetto, R J Zaino, N M Spirtos, J D Bloss, A Pearlman, M A Maiman,JG Bell. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study.*Gynecologic Oncology 2004;*92: 744-751
11. Blake P, Swart AM, Orton J, Kitchener H, Whelan T, Lukka H, Eisenhauer E, Bacon M, Tu D, Qian W et al. ASTEC/EN.5 Study Group. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet* 2009 10;373(9658):137-46
12. Aalders J, Abeler V, Kolstad P, Onsrud M, Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol*: 1980;56(4):419-27.
13. Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A comparison of the Charlson co-morbidity index derived from medical record data and administrative billing data. *Journal of clinical epidemiology* 1999;**52**:137-42.
14. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Critical reviews in oncology/hematology* 2005;**55**:231-40.
15. Zuurendonk LD, Smit RA, Mol BW, et al. Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. *Eur J Surg Oncol* 2006;**32**:450-4.
16. Working Group Gynaecologic Oncology. http://www.oncoline.nl. retrieved 2007.
17. Vulto AJ, Lemmens VE, Louwman MW, et al. The influence of age and co-morbidity on receiving radiotherapy as part of primary treatment for cancer in South The Netherlands, 1995 to 2002. *Cancer* 2006;**106**:2734-42.
18. Lemmens VE, Janssen-Heijnen ML, Verheij CD, Houterman S, Repelaer van Driel OJ, Coebergh JW. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. *The British journal of surgery* 2005;**92**:615-23.
19. Bastiaannet E, Liefers GJ, de Craen AJ, et al. Breast cancer in elderly compared to younger patients in The Netherlands: stage at diagnosis, treatment and survival in 127,805 unselected patients. *Breast cancer research and treatment*;**124**:801-7.
20. Hamaker ME, Schreurs WH, Uppelschoten JM, Smorenburg CH. Breast cancer in the elderly: retrospective study on diagnosis and treatment according to national guidelines. *The breast journal* 2009;**15**:26-33.
21. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *International journal of cancer* 2007;**120**:1986-92.

22. Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. *Int J Gynecol Cancer* 2007;**17**:441-6.
23. Boice JD, Jr., Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiation research* 1988;**116**:3-55.
24. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 1993;**11**:485-90.
25. Louwman WJ, Aarts MJ, Houterman S, van Lenthe FJ, Coebergh JW, Janssen-Heijnen ML. A 50% higher prevalence of life-shortening chronic conditions among cancer patients with low socioeconomic status. *British journal of cancer.*
26. J C. Pavelka, I Ben-Shachar, J M. Fowler, N C. Ramirez, L J. Copeland, L A. Eaton, T P. Manolitsas, D E. Cohn. Morbid obesity and endometrial cancer: surgical, clinical, and pathologic outcomes in surgically managed patients. *Gynecologic Oncology;*2004 95*:* 588-592
27. E. Everett, H. Tamimi and B. Greer et al. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer, *Gynecol. Oncol.* **90** (2003), pp. 150–157

3.2

Effect of diabetes on endometrial cancer recurrence and survival

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Abstract

Objective

The purpose of this study was to investigate the influence of diabetes mellitus (DM) on cancer stage at diagnosis, cancer recurrence, and survival of endometrial cancer (EC) patients and the influence of the treatment of EC on glycaemic control, treatment, and complications of DM.

Methods

In this retrospective cohort study all 1,644 patients with EC newly diagnosed in 2000-2008 and recorded in the population-based Eindhoven Cancer Registry (ECR) were included. In addition, in this total cohort a sub cohort was selected for additional analyses, including193 EC patients with DM and a matched sample of 195 EC patients without DM. Patients with FIGO stage IV as well as non-endometrioid histology were excluded.

Results

EC patients with DM had a significantly higher age (69 years vs. 64 years), higher FIGO stages, higher body mass index (BMI) (34 kg/m^2 vs. 30 kg/m^2), lower socioeconomic status (SES), and more comorbidities compared to EC patients without DM. In contrast, EC was not significantly associated with changes in DM characteristics in time. The 5-year overall survival rate for EC patients with DM was significantly lower than for EC patients without DM (68% vs. 84%), after adjusting for age, stage, period of diagnosis, cardiovascular disease, and treatment, this significant effect of DM on overall mortality persisted (HR 1.4, 95% CI: 1.0-1.8). On the contrary, for EC-specific mortality (n=388) no statistically significant effect of DM was observed after adjustment for FIGO stage (HR = 1.7, 95% CI: 0.7-3.9).

Conclusions

EC patients with DM compared to those without had worse patient characteristics, similar recurrence rates, a higher FIGO stage and overall mortality.

Introduction

Endometrial cancer (EC), the most common of gynaecological malignancies, is suggested to be biologically associated with diabetes mellitus (DM), since shared risk factors, such as physical inactivity, obesity as well as high-saturated diet, only partly explain the observed higher risk of EC in DM patients [1-6]. Although the effect of DM on cancer risk may be small, given the high incidence of both DM and EC [7-9], even a modest association between DM and cancer means a considerable effect on public health. Furthermore, the number of newly diagnosed cancer patients with DM is expected to even double from 5,500 in 2000 to 10,400 in 2015 [10].

In addition, many studies showed that EC patients with pre-existing DM had a significantly increased overall mortality, while only one study investigated the effect of DM on EC-specific mortality [11-16]. This study found no effect of DM on EC-specific mortality, however, numbers of DM patients and deaths were small, and information about treatment of EC was missing [12]. The treatment of EC may effect glycaemic control, treatment, and complications of DM as well, whereas studies investigating this effect are lacking.

The potential biological link between the two diseases is incompletely understood and the mediators for this association are not known, but are thought to be related to hyperinsulinaemia (either due to insulin resistance or due to administered insulin), hyperglycaemia, insulin-like growth factor, and adipocytokines [3]. Moreover, evidence from observational studies suggest that some oral glucose lowering medications used to treat hyperglycaemia are associated with either increased or reduced cancer risk and mortality [17, 18].

The purpose of the present study was to investigate whether EC patients with DM had a different stage at diagnosis, were treated differently, had different recurrence rates, and worse overall and EC-specific survival compared to EC patients without DM. In view of the association between EC and DM, the effect of treatment of EC on glycaemic control, treatment, and complications of DM was investigated as well.

Methods

The Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre South (CCCS), records data on all patients newly diagnosed with cancer in the southern part of The Netherlands, an area with 2.4 million inhabitants. The registry is notified by six pathology departments, hospital medical records offices in 10 community hospitals, and two large radiotherapy institutes.

Data on patient characteristics such as date of birth and postal code, as well as tumour characteristics such as date of diagnosis, tumour type, histology, stage, and initial treatment are routinely extracted from medical records by trained registrars. The guideline for initial

treatment of EC patients in the ECR region is described elsewhere [19, 20]. Comorbidity is obtained from the medical records according to an adapted version of the Charlson Comorbidity Index [21]. Comorbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis. Medication use served as indicator for active disease; comorbidity was registered when described in the medical record. DM included both type 1 and type 2 disease and was registered as a dichotomous variable (yes/no), as were all other concomitant conditions. Tumour site and morphology were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O) [22]. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, was provided at an aggregated level for each postal code [23]. Information about vital status was obtained from the municipal personal records database (GBA) for all EC patients included in this study.

Total cohort

For this retrospective cohort study we included all patients with EC, newly diagnosed between 2000 and 2008 from the ECR (figure 1). Patients with endometrioid EC were selected because this type of EC is oestrogen driven and related to risk factors, like obesity, hyperinsulinaemia, and DM [24]. We selected all patients with FIGO stages I, II, and III, according to the International Federation of Gynaecology and Obstetrics (FIGO, 1988) [25]. FIGO stage IV (n=58) was excluded because treatment differed with other FIGO stages and no effect of DM on prognosis was seen for this subgroup in earlier studies as well [15]. After selection a total of 255 EC patients with DM and 1,389 EC patients without DM remained for the total cohort analyses (figure 1).

Sub-cohort

Out of the total cohort we selected a sub-cohort. Seven hospitals in the ECR region consented to provide additional in-depth data, including 193 EC patients with DM and 195 age-matched EC patients without DM for in-depth analyses. Matching for age was randomly performed according to 5-year age groups.

For the sub-cohort analysis additional information was collected from the Registration System Oncological Gynaecology (ROGY), a web-based patient information system, maintained since 2006 by gynaecologists in the CCCS area [26]. Information about follow-up, including recurrent disease, is registered in this system. Furthermore, we linked these registries with Pharmo RLS (Institute for Drug Outcomes Research) in order to obtain information about laboratory tests, medication, and hospitalization [27].

We also recorded BMI, smoking status, information about complications of radiotherapy, and DM status from the medical charts for sub-cohort analysis. DM status included type of DM, date of onset, and the presence of complications due to DM. These complications were registered as microvascular (retinopathy, nephropathy, and neuropathy) and macro-vascular complications (coronary disease and peripheral arterial disease). To study the

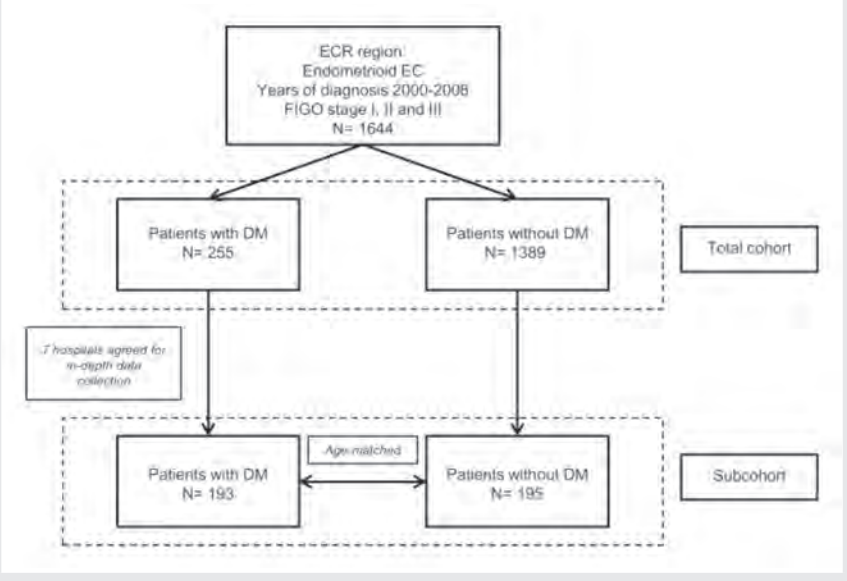

Figure 1 Flowchart of the selection of endometrial cancer patients for the total cohort and sub-cohort

DM, diabetes mellitus; EC, endometrial cancer; ECR, Eindhoven Cancer Registry

effect of EC on the regulation of DM, Hba1C values, DM medication, and DM complications were registered in the year before diagnosis and the year after diagnosis of EC.

Information about recurrence rate and cause of death was collected from the medical records for the sub-cohort analysis. Recurrence was defined as the existence of local (vaginal cuff) or regional recurrence (pelvis), or metastatic disease (lymph nodes and organs). Cause of death was obtained from the medical record when possible, otherwise it was determined by contacting the general practitioner.

Statistical analysis

The SAS computer package (version 9.2) was used for all statistical analyses (SAS Institute, Cary, NC, 1999). A p-value <0.05 was regarded as statistically significant.

Differences between EC patients with and without DM in the total cohort and sub-cohort were analysed using chi square and the t-test when applicable.

Overall survival analysis of the total cohort and sub-cohort was analysed using the life-table method to evaluate prognosis after diagnosis of EC for patients with or without DM. Survival time was defined as the time from diagnosis to death or January 1, 2010 for

the patients who were still alive. In the total cohort, survival was also analysed according to FIGO stage at diagnosis and DM status.
The independent prognostic effect of DM on overall survival of EC patients was estimated using Cox proportional hazard analyses. The effect of DM over time satisfied the assumption of proportionality since the graphs of the log(log(survival)) versus log of survival time resulted in graphs with parallel lines. The hazard rates for death of EC patients with DM compared to EC patients without DM, in the total cohort and sub-cohort, were further adjusted for age, stage, period of diagnosis, specific comorbidities, and treatment. In addition, in the sub-cohort EC-specific survival and recurrence free survival was analysed. EC-specific survival was analysed using the life-table method to evaluate prognosis after diagnosis of EC, with EC-specific death as event, while censoring other causes of death. The hazard rates for death due to EC, comparing EC patients with and without DM, were further adjusted for stage. Recurrence free survival of EC patients with DM compared to without DM was analysed as well. This survival was defined as time to the first recurrence or death from any cause, whichever occurred first.

Results

Total cohort

In the period 2000-2008, 1,644 women were diagnosed with EC, 255 (16%) of whom had DM at cancer diagnosis. EC patients with DM were on average 5 years older, diagnosed more often with a higher FIGO stage, and a lower SES (Table 1). Cardiovascular disease, hypertension, cerebrovascular disease, and pulmonary disease were more often present in EC patients with DM compared to EC patients without DM. While EC patients with DM received surgery with lymphadenectomy less often, they received radiotherapy more often compared to EC patients without DM. Although not statistically significant, EC patients with DM received brachytherapy more often and had fewer complications due to radiotherapy (49% vs. 72%, not shown) than patients without DM. Moreover, the number of positive lymph nodes did not differ between both groups (Table 1).
At the end of follow-up, out of the total cohort 82 (31%) EC patients with DM died compared to 228 (16%) without DM. The 5-year overall survival rate for EC patients with DM was significantly lower than for EC patients without DM (68% vs. 84%), in figure 2 overall survival rates for the different FIGO stages are shown. After adjusting for age, stage, period of diagnosis, specific comorbidities, and treatment, this significant effect of DM on overall survival persisted (HR 1.3, 95% CI: 1.0-1.8) (Table 3).

Sub-cohort

The patient characteristics of the sub-cohort of 388 EC patients were almost identical to those in the total cohort. In the sub-cohort, with EC patients of 6 selected hospitals, the

Table 1 Characteristics of patients with EC FIGO stage I-III according to DM status (*n* =1644)

	Total cohort (*n* = 1644)				Sub cohort (*n* = 388)			
	Without DM *N* = 1389		With DM *N* = 255		Without DM *N* = 195		With DM *N* = 193	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Mean age (± SD)	64	(± 10.3)	69	(± 9.1)**	69	(± 8.5)	70	(± 9.0)
FIGO stage [a]								
I	1158	(83)	190	(75)	160	(82)	135	(70)
IA	187	(16)	23	(12)	22	(14)	19	(14)
IB	610	(53)	97	(51)	75	(47)	68	(50)
IC	350	(31)	69	(37)	63	(39)	48	(36)
II	103	(8)	28	(11)	11	(6)	24	(12)
III	128	(9)	37	(14)*	24	(12)	34	(18)*
Grade EC [a]								
I	588	(44)	113	(45)	68	(37)	81	(43)
II	546	(41)	96	(39)	80	(44)	71	(38)
III	191	(15)	41	(16)	35	(19)	36	(19)
Socioeconomic status [a]								
Low	331	(24)	92	(37)	56	(29)	76	(41)
Middle	532	(39)	91	(37)	74	(38)	66	(35)
High	442	(33)	50	(20)	56	(29)	32	(17)
Institutionalized	59	(4)	15	(6)**	7	(4)	13	(7)*
Comorbidities[a]								
Cardiovascular disease	180	(15)	83	(33)**	44	(23)	68	(35)*
Hypertension	359	(30)	142	(56)**	77	(40)	111	(57)*
Cerebrovascular disease	32	(3)	17	(7)*	5	(3)	16	(8)*
Pulmonary disease	54	(5)	21	(8)*	7	(4)	19	(10)*
Previous cancer	159	(13)	35	(14)	28	(14)	28	(14)
Received surgery	1373	(99)	250	(98)	192	(98)	188	(97)
Type of surgery								
With lymphadenectomy	421	(30)	57	(22)	67	(34)	57	(30)
Positive lymph nodes	34	(8)	5	(9)	5	(7)	5	(9)
Without lymphadenectomy	968	(70)	198	(78)*	128	(66)	136	(70)

[a] Does not add up to total due to missings, percentages determined for available data;
* *p*-value < 0.05; ** *p*-value < 0.0001
DM, diabetes mellitus; EC, endometrial cancer

Table 1 Continued

	Total cohort (*n* = 1644)				Sub cohort (*n* = 388)			
	Without DM *N* = 1389		With DM *N* = 255		Without DM *N* = 195		With DM *N* = 193	
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)
Received chemotherapy	27	(2)	2	(1)	2	(1)	1	(1)
Received radiotherapy	384	(28)	98	(38)*	62	(32)	73	(38)
Type of radiotherapy								
External beam radiotherapy	227	(16)	56	(22)	38	(19)	38	(20)
Brachytherapy	70	(5)	24	(9)	9	(5)	18	(9)
Combination	79	(6)	15	(6)	13	(7)	14	(7)
BMI (kg/m^2, ± SD)[a]	n.a.				30.1	(± 6.7)	33.7	(± 7.3)*
<25					56	(50)	42	(33)
30-35					30	(27)	36	(29)
>35					26	(23)	47	(38)*
Smoking status [a]	n.a.							
Yes					11	(11)	14	(14)
No					76	(75)	81	(79)
Quit					14	(14)	8	(8)

[a] Does not add up to total due to missings, percentages determined for available data;
* *p*-value < 0.05; ** *p*-value < 0.0001
DM, diabetes mellitus; EC, endometrial cancer

percentage of EC patients who received lymphadenectomy was higher compared to the percentage in the total cohort (table 1). The in-depth data showed that EC patients with DM were diagnosed more often with a higher BMI compared to EC patients without DM, while smoking status did not differ between the two groups (Table 1). The average duration of DM was 9 years and 9 patients were diagnosed with DM in the year before or at diagnosis of EC (Table 2). Mean HbA1c values, BMI, and number of patients using medication remained almost similar in the year before and up to one year after diagnosis of EC. Sixty patients (31%) had one or more DM-related complications at the time of EC diagnosis and after EC diagnosis, 17 patients, without complications before diagnosis, developed micro- or macrovascular complications (Table 2).

In the survival analysis of the sub-cohort, the 5-year overall survival rate for EC patients with DM was significantly lower than for EC patients without DM (65% vs. 85%). After adjusting for age, stage, period of diagnosis, specific comorbidities, and treatment, this significant effect of DM on overall survival persisted (HR 2.3, 95% CI: 1.4-3.7) (Table 3). On

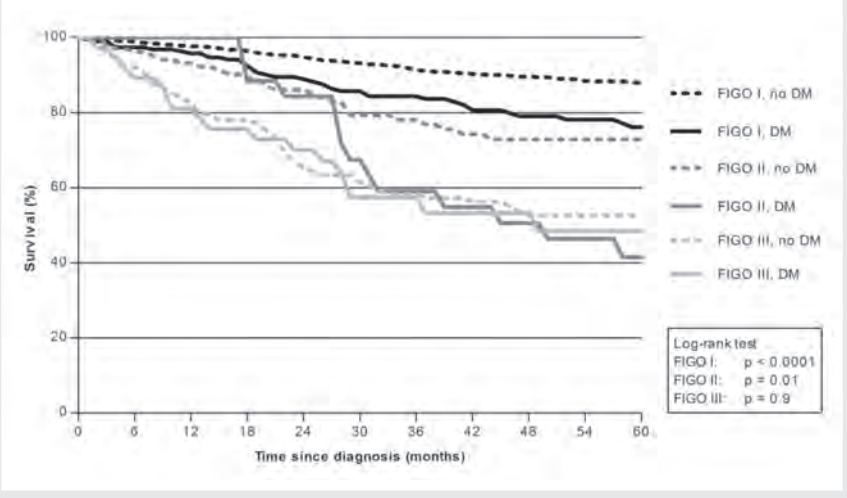

Figure 2 Overall survival of EC patients according to DM status and FIGO stage.

DM, diabetes mellitus; EC, endometrial cancer

the contrary, for EC-specific mortality (n=388) no statistically significant effect of DM was observed after adjustment for FIGO stage (HR = 1.4, 95% CI: 0.7-2.6) (Table 3 and Figure 3). Although not statistically significant, evaluation of the cause of death showed that EC patients with DM died of comorbidity most often (n=33, 54%), whereas EC patients without DM died of EC (n=16, 57%) most often. Comorbidity included all different types of comorbid diseases present in the Charlson Comorbidity Index. In the group of comorbidities, cardiovascular and cerebrovascular disease were the most common causes of death in EC patients with and without DM.

In the selected sub-cohort recurrent disease was found in 26 (14%) EC patients with DM compared to 27 (14%) without DM. Metastasis was the most frequent type of recurrence and was observed in 9% of EC patients with DM and 8% of EC patients without DM. Recurrence free survival was significantly lower for EC patients with DM compared to those without (p = 0.0001). However, the difference between overall survival and recurrence free survival, was approximately the same for patients with and without DM. The recurrence did not differ between EC patients with and without DM, while the overall survival did differ strongly between both groups.

Table 2 DM characteristics before and after diagnosis of EC for patients with DM at cancer diagnosis (n = 388)

	Before diagnosis [a] N = 193		After diagnosis [b] N = 193	
	N	(%)	N	(%)
DM type				
1	2	(1)		
2	191	(99)		
DM length at diagnosis (years, ± SD)	8.7	± 7.7		
<1	9	(5)		
1	7	(4)		
2-5	41	(21)		
5-10	40	(21)		
>10	45	(23)		
Unknown	51	(26)		
BMI mean (kg/m^2, ± SD)	34.1	± 6.9	33.3	± 6.7
Hba1c mean (%,± SD)	7.6	± 1.3	7.5	± 1.3
Medication				
Oral glucose-lowering	105	(55)	99	(51)
Insulin	22	(11)	24	(13)
Diet	2	(1)	1	(1)
Oral glucose-lowering and insulin	38	(20)	47	(24)
No medication	3	(1)	2	(1)
Unknown	23	(12)	20	(10)
Complications				
Microvascular	8	(4)	11	(6)
Macrovascular	41	(21)	49	(25)
Both	10	(5)	15	(8)
No complications	92	(48)	76	(39)
Unknown	42	(22)	42	(22)

[a] In the year before diagnosis of EC, until diagnosis.
[b] From diagnosis of EC, until 1 year after diagnosis.
DM, diabetes mellitus; EC, endometrial cancer

Table 3 Multivariate regression analysis of the effect of diabetes on all-cause mortality and EC-specific mortality

	Total cohort (n = 1644)		Sub cohort (n = 388)			
	All-cause mortality [a]		All-cause mortality [a]		EC-specific mortality [b]	
	HRR [c]	(95% CI)	HRR [c]	(95% CI)	HRR [c]	(95% CI)
DM						
Yes	1.3	(1.0-1.8)*	2.3	(1.4-3.7)*	1.4	(0.7-2.6)
No	1.0		1.0		1.0	
Age	1.1	(1.1-1.1)**	1.1	(1.0-1.1)**		
FIGO						
Stage I	1.0		1.0			
Stage II	2.0	(1.4-2.9)*	2.0	(1.1-3.7)*	6.9	(3.1-15.4)**
Stage III	3.7	(2.7-5.2)**	3.8	(2.1-6.8)**	8.7	(4.3-17.5)**
Period of diagnosis	1.0	(0.9-1.1)	1.0	(1.0-1.2)		
Comorbidities [d]						
Cardiovascular disease	0.9	(0.7-1.3)	0.9	(0.6-1.6)		
Hypertension	0.9	(0.7-1.3)	0.8	(0.5-1.3)		
Cerebrovascular disease	2.0	(1.2-3.3)*	2.5	(1.2-5.1)*		
Pulmonary disease	1.3	(0.8-2.1)	1.1	(0.5-2.5)		
Previous cancer	1.7	(1.2-2.3)*	1.0	(0.6-1.8)		
Surgery						
Yes	1.0		1.0			
No	3.4	(2.0-5.7)**	4.1	(1.7-9.8)*		
Radiotherapy						
Yes	1.0		1.0			
No	1.0	(0.7-1.3)	1.5	(0.9-2.4)		

[a] Proportional hazards model for all-cause mortality is adjusted for DM, age at time of diagnosis, FIGO stage, period of diagnosis, cardiovascular disease, hypertension, cerebrovascular disease, pulmonary disease, previous cancer, surgery, and radiotherapy.

[b] Proportional hazards model for EC-specific mortality is adjusted for DM and FIGO stage.

[c] HRR = Hazard Rate Ratio, missing values were included in the multivariate analysis, but not shown in the table

[d] The reference for a specific comorbidity is the absence of the specific comorbidity

* p-value < 0.05; ** p-value < 0.0001

DM, diabetes mellitus; EC, endometrial cancer

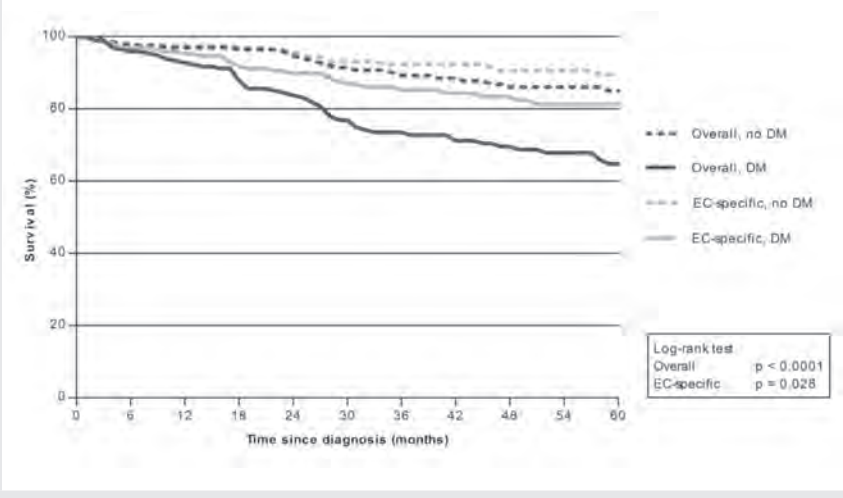

Figure 3 Overall and EC-specific survival of EC patients according to DM status.

DM, diabetes mellitus; EC, endometrial cancer

Discussion

In the present study, we found that EC patients with DM had a significantly higher overall mortality than those without DM. In addition, DM was not associated with higher recurrence rates, or a higher EC-specific mortality after adjustment for the observed higher FIGO stages found for patients with DM. DM treatment and DM complications did not change significantly when patients were compared before and after EC diagnosis and treatment.

Previous studies have already identified DM as a prognostic factor for EC in postmenopausal patients [11-16]. In one of these, a Dutch population-based study, the hazard ratio was 1.4 (95% CI: 1.1-1.8)), while in another study of 93 DM patients a HR of 1.7 (95% CI: 1.1-2.5) was found when comparing EC patients with and without DM [12, 15]. However, in these studies no association between EC-specific mortality and DM was found. Cause of death has never been properly investigated for patients with EC, making it difficult to understand whether the observed increased overall mortality can simply be explained by an effect of DM or is a true effect due to interaction between the two diseases.

While in our study EC patients with DM had a higher FIGO stage at diagnosis compared to patients without DM, in other studies baseline DM was not associated with the extent of disease at EC diagnosis [13, 14]. At diagnosis the tumour has infiltrated the myometrium, causing postmenopausal blood loss as first symptom in 95% of EC patients, these symptom might be overshadowed by symptoms of comorbidities or ignored in DM patients [28]. In contrast, we hypothesized that DM effects myometrial invasion directly by a proliferative or anti-apoptotic effect, resulting in blood loss in a more advanced stage. This myometrial invasion may be effected by adipokines, which are adipocyte-secreted hormones, as well [29, 30]. The plasma concentrations of adiponectin, one of the most abundant adipokines, are reduced in obese individuals and interestingly have been reported to have anticarcinogenic properties either. Furthermore, in vitro studies have shown that adiponectin may inhibit cell proliferation and induce apoptosis of some cancer cells, which may explain why EC patients with DM, and a significant higher BMI and lower adiponectin concentrations, have a more advanced tumour stage than their counterparts [29, 30]. Other underlying biological factors are oestrogen, insulin, and the free related insulin-like growth factor-I (IGF-I), which may influence the effect of DM on EC [3, 5]. Cancer proliferation might be stimulated by this free IGF-I, a biologically active form of growth factor [3]. Moreover, many cancer cells have an increased insulin receptor content, therefore insulin could favour cancer progression and facilitate the growth of tumours and early infiltration [3, 31]. In contrast with insulin, the DM drug metformin is thought to be a potent inhibitor of cell proliferation in EC, thereby reducing cancer risk [32]. Whether the underlying mechanism for this effect is related to the systemic action of this drug, by reducing circulating insulin levels, or a direct action on cancer cells is still unknown[32].

Although the rapid tumour growth by insulin could explain the more advanced FIGO stages, an effect on presence of recurrence should than be expected as well. Even though our EC-specific survival analysis showed no effect of DM after adjusting for this more advanced tumour stage, another study did observe lower EC-specific survival for EC patients with DM [13]. However, this study analysed only a small group of 42 EC patients with DM and no stratification for FIGO stage was made [13]. Another important study, with 12,000 EC patients, investigated the impact of race and comorbidity on EC-specific survival, thereby adjusting for patients, tumour, and treatment characteristics[33]. DM was associated with poorer survival in white women, but not in blacks[33].

In our study the hypothesis that EC has an negative effect on the course of DM can be rejected when comparing values one year before and up to one year after diagnosis of EC. Although assuming that when a patient has EC, attention for DM control decreases, EC itself might have an effect on DM. In contrast, weight loss due to cancer, cancer therapy, and eating less, may improve DM control. In the contrary, many breast cancer patients

gain weight after diagnosis, resulting in a dysregulation of DM [34]. Since all of the above-mentioned hypotheses may affect DM status in different ways, an overall effect could possibly be camouflaged.

A limitation of the current study is the retrospective study design, therefore only information available in the medical records could be collected, BMIs and HbA1c values were not always reported. The BMI was missing in 39% of the EC patients in the sub-cohort. Furthermore, detailed information on DM medication was missing, which could be of interest when investigating the specific effect of metformin on survival in EC patients. A significant effect of DM on EC-specific mortality was not found, however, the additional analysis for EC-specific mortality was underpowered due to the relatively small number of patients in the sub-cohort. Therefore, the possible effect of DM on FIGO stage and EC-specific mortality has to be further investigated in a larger group of patients.

In summary, this study supports the hypothesis that EC patients with DM have worse survival rates than EC patients without DM. Higher FIGO stages and more comorbidities in EC patients with DM could explain these survival rates. Future studies are needed to reveal the relationship between DM and EC, explaining the late onset of symptoms in EC patients with DM compared to EC patients without DM. The higher mortality rates for EC patients with DM were most likely caused by DM as such, therefore, physicians should be encouraged and motivated to rigorously treat and follow these patients with DM also after the EC diagnosis and treatment. Furthermore, postmenopausal women with the combination of DM and EC might have a more advanced stage at EC diagnosis, causing a higher EC-specific mortality, so caution is recommended for this subgroup.

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References

[1] Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. *Gynecol Oncol* 2009;**114**(1):121-7.

[2] Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007;**50**(7):1365-74.

[3] Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010;**60**(4):207-21.

[4] Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *Br J Cancer* 2008;**98**(9):1582-5.

[5] Wedisinghe L, Perera M. Diabetes and the menopause. *Maturitas* 2009;**63**(3):200-3.

[6] Bray F, Dos Santos Silva I, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. *Cancer Epidemiol Biomarkers Prev* 2005;**14**(5):1132-42.

[7] Sloan FA, Bethel MA, Ruiz D, Shea AM, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. *Arch Intern Med* 2008;**168**(2):192-9; discussion 199.

[8] Cancer in The Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8.

[9] Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, Hamberg-van Reenen HH, Verkleij H, Heus S, Melse JM. Diabetes tot 2025; preventie en zorg in samenhang. *RIVM-rapport 260322004* 2009.

[10] Cancer in The Netherlands (2004) Trends, prognoses and implications for healthcare. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-13-0.

[11] Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; **300**(23):2754-64.

[12] Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. *Int J Gynecol Cancer* 2007;**17**(2):441-6.

[13] Folsom AR, Anderson KE, Sweeney C, Jacobs DR, Jr. Diabetes as a risk factor for death following endometrial cancer. *Gynecol Oncol* 2004;**94**(3):740-5.

[14] Steiner E, Eicher O, Sagemuller J, Schmidt M, Pilch H, Tanner B, Hengstler JG, Hofmann M, Knapstein PG. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. *Int J Gynecol Cancer* 2003;**13**(2):197-203.

[15] van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer* 2007;**120**(9):1986-92.

[16] Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern The Netherlands 1995-2008. *Eur J Cancer* 2011;**47**(10):1504-10.

[17] Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. *Diabetologia* 2012;**55**(6):1607-1618.

[18] Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. *Diabetologia* 2012;**55**(6):1619-1632.

[19] Zuurendonk LD, Smit RA, Mol BW, Feijen HW, de Graaff J, Sykora D, de Winter KA, vd Wurff A, Snijders MP, Kruitwagen RF. Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. *Eur J Surg Oncol* 2006;**32**(4):450-4.

[20] www.oncoline.nl. National Dutch guideline of endometrial cancer. 2011.

[21] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**(5):373-83.

[22] International Classification of Diseases of Oncology. Version 2007; first edition Geneva: WHO, 1976.

[23] van Duijn C, Keij I. Sociaal-economische status indicator op postcode niveau. *Maandstatistiek van de bevolking* 2002;**50**(2):32-35.

[24] Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983;**15**(1):10-7.
[25] Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet* 2006;**95 Suppl 1**:S105-43.
[26] Boll D, Hermans RHM, Keijser KGG, van der Putten HWHM, Vos MC, Kruitwagen RFPM, van den Eijnden-van Raaij AJM, van Eenbergen MCHJ. Nuttige Diensten van Regionaal EPD, Bundeling Regionale Expertise Gynaecologische Oncologie. *Medisch Contact* 2009;**64**(21):942-945.
[27] van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, Herings RM. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. *Eur J Cancer* 2010;**46**(2):395-404.
[28] Kurman RJ, Ellenson LH, Ronnett BM. *Blaustein's Pathology of the Female Genital Tract*. 6th ed. New York, NY: Springer-Verlag; 2011.
[29] Moon HS, Chamberland JP, Aronis K, Tseleni-Balafouta S, Mantzoros CS. Direct role of adiponectin and adiponectin receptors in endometrial cancer: in vitro and ex vivo studies in humans. *Mol Cancer Ther* 2011;**10**(12):2234-43.
[30] Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, Rinaldi S, Dossus L, Slimani N, Lundin E, Tjonneland A, Olsen A, Overvad K, Clavel-Chapelon F, Mesrine S, Joulin V, Linseisen J, Rohrmann S, Pischon T, Boeing H, Trichopoulos D, Trichopoulou A, Benetou V, Palli D, Berrino F, Tumino R, Sacerdote C, Mattiello A, Quiros JR, Mendez MA, Sanchez MJ, Larranaga N, Tormo MJ, Ardanaz E, Bueno-de-Mesquita HB, Peeters PH, van Gils CH, Khaw KT, Bingham S, Allen N, Key T, Jenab M, Riboli E. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab* 2007;**92**(1):255-63.
[31] Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr Relat Cancer* 2009;**16**(4):1103-23.
[32] Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation--implications for a novel treatment strategy. *Gynecol Oncol* 2010;**116**(1):92-8.
[33] Olson SH, Atoria CL, Cote ML, Cook LS, Rastogi R, Soslow RA, Brown CL, Elkin EB. The impact of race and comorbidity on survival in endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 2012;**21**(5):753-60.
[34] Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer* 2012;**118**(8 Suppl):2277-87.

4

Quality of life

4.1

Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study

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Abstract

Purpose

Routine lymphadenectomy (LA) in early stage endometrial cancer does not improve survival. However, in the absence of lymph node metastasis, radiotherapy (RT) could be withheld and hence could result in less morbidity. Our aim was to evaluate health related quality of life (HRQL) in endometrial cancer survivors that received routine pelvic LA without RT compared to no LA, but RT in the presence of risk factors.

Patients and Methods

Stage I-II endometrial cancer survivors diagnosed between 1999 and 2007 were selected from the Eindhoven Cancer Registry. Survivors completed the SF-36 and the EORTC-QLQ-EN24. ANCOVA and multiple linear regression analyses were applied.

Results

742 (77%) of the endometrial cancer survivors returned a completed questionnaire. 377 (51%) had received no LA nor RT (LA-RT-), 198 (27%) had received LA+RT-, 153 (21%) LA-RT+ and 14 patients (2%) had received both. Twenty-two percent of LA+ women reported a heavy feeling in one or both legs, compared to 13% of women without LA, as well as higher lymfedema symptom scores (25 vs. 20, p=0.04). Sixteen percent of women with external beam RT reported diarrhea symptoms, compared to 5% of women who received no RT, and 3% of women who received brachytherapy only. Women who were treated with RT reported higher gastrointestinal symptoms scores vs. those who did not (23 vs. 16, p=0.04). HRQL was comparable between all four treatment groups.

Conclusion

Despite distinct symptom patterns among women who received LA or RT, no clinically relevant differences in HRQL were observed when compared to women not receiving adjuvant therapy. Using LA to tailor adjuvant pelvic radiotherapy and prevent over-treatment in low-risk patients cannot be recommended.

Introduction

Endometrial carcinoma is the most frequent gynecological cancer in the Western world with an incidence of 15-25 per 100.000 women per year.[1,2] More than 75% of the endometrial cancers are diagnosed at an early stage, resulting in overall good prognosis, with a 5-year overall survival rate of 80% in the US and the Netherlands.[1,2] On January 1, 2008, in the United States there were approximately 573,300 women alive with a history of cancer of the uterine corpus, compared to 18,000 on January 1, 2010 in the Netherlands.[2]
The role and degree of lymphadenectomy and the use of postoperative external beam radiotherapy in early stage endometrial cancer are among the most controversial issues in gynecologic oncology.[3] The results of two randomized trials comparing routine pelvic lymphadenectomy to no lymphadenectomy in early stage endometrial cancer,[4,5] as well as a meta-analysis,[6] showed that routine lymphadenectomy improved surgical staging but did not result in improved survival. However, these studies are limited by the fact that HRQL was not measured.[6] Other than survival, lymphadenectomy may contribute in the selection of patients that could be withheld additional radiotherapy and hence prevent unnecessary over-treatment or inappropriate under-treatment.[3] This is important as one of the major concerns of adjuvant treatments is the risk of morbidity, and it is known that external beam radiotherapy (EBRT) can impact HQRL up to years after diagnosis.[7-9] Unfortunately, information is poor regarding morbidity and HRQL after lymphadenectomy, and mostly based on chart review,[10] or clinical reports.[4,5]
In order to compare the treatment strategy of routine lymphadenectomy without EBRT in the absence of lymph node metastasis with the treatment strategy of no lymphadenectomy and the application of EBRT in the presence of risk factors we performed a cross-sectional, population-based study of HRQL and symptoms of early stage endometrial cancer survivors. Based on the low prevalence of lymphedema morbidity[4,5,10] and the well known long term effects of EBRT,[7-9] we hypothesized that women undergoing pelvic lymphadenectomy would overall report a better HRQL compared to women who did not, but were administered EBRT in the presence of risk factors.[11] If our hypothesis is found to be true, the role of lymphadenectomy as a diagnostic tool would be important in low-risk cases, if only to prevent over-treatment, and consequently result in a better HRQL and fewer symptoms.

Methods

Setting and participants

The Comprehensive Cancer Center South comprises 10 hospitals in the southern part of The Netherlands. One hospital did not participate in this study. Since 1998, five hospitals in the West region recommend routine pelvic lymphadenectomy in women with apparently early stage endometrial cancer.[12] When pelvic lymphadenectomy was performed, external

beam radiotherapy (EBRT) was administered only to patients with lymph-node metastases. The other four hospitals (East) did not perform routine pelvic lymphadenectomy but administered radiotherapy in the presence of risk factors.[11] In this cross-sectional study the HRQL and symptoms of endometrial cancer survivors registered with the Eindhoven Cancer Registry (ECR) were evaluated for both treatment strategies ('East' and 'West').
The ECR compiles data of all individuals newly diagnosed with cancer in an area with 10 hospitals serving 2.3 million inhabitants[13]. For this study, all individuals diagnosed with endometrial cancer FIGO stage I-II (classification 1988) between 1999 and 2007 were eligible for participation. In the period 2002-2006 a few patients were enrolled in the PORTEC-2 trial in which patients with stage I endometrial carcinoma with features of high-intermediate risk or IIA (apart from grade 3 with greater than 50% myometrial invasion) were randomly assigned to EBRT or vaginal brachytherapy.[14]
Patients with unverifiable addresses or died prior to start of study were excluded. Data collection started in 2009. A local certified Medical Ethics Committee approved the study.

Data collection

Cancer survivors were informed about the study by a letter from their attending gynecologist. The letter explained that by completing and returning the enclosed questionnaire, survivors consented to participate in the study and agreed to the linkage of the questionnaire data with their disease history in the ECR. Non-respondents were sent a reminder letter and questionnaire within 2 months.

Measures

Survivors' socio-demographic and clinical information were available from the ECR. The ECR routinely collects data on tumor characteristics, including date of diagnosis, tumor stage and grade according to the Tumor-Node-Metastasis clinical classification,[15] treatment, and patient background characteristics including date of birth and comorbidity at the time of diagnosis. Follow-up data on recurrence and metastasis were derived from chart records.
Comorbidity at the time of survey was categorized according to the Self-administered Comorbidity Questionnaire (SCQ).[16] Socioeconomic status was determined by an indicator developed by Statistics Netherlands[17]. Body mass index (BMI), marital status, educational level, employment status and smoking were also assessed.

General HRQL was assessed with the validated Dutch version of the SF-36 questionnaire.[18] All scales were converted to a 0-100 linear scale according to standard scoring procedures. Higher scores indicate better HRQL. Disease-specific HRQL was assessed with the Dutch validated European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Endometrial Cancer Module (EORTC QLQ-EN24).[19] This questionnaire assessed symptom burden (lymphedema, urological symptoms, gastrointestinal symptoms,

body image and sexual/vaginal symptoms, back/pelvic pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity, and sexual enjoyment). All scales were converted to a 0-100 linear scale according to standard scoring procedures. Higher scores indicated higher symptom burden.

Statistical analyses

All statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC). Differences in demographic and clinical characteristics between treatment groups were compared with chi-square test on categorical variables and t-test for continuous variables.

The SF-36 and EORTC QLQ-EN24 mean scores of the different treatment groups were compared with analyses of covariance (ANCOVA). Confounding background variables included for adjustment in these analyses were determined *a priori*:[20] age at survey, stage of cancer, grade of cancer, years since diagnosis, marital status, BMI, education, socio-economic status, comorbidity.

Multiple linear regression models investigated the association between HRQL, symptoms and a range of sociodemographic and clinical variables. Multicollinearity was determined if the variance inflation factor (VIF) was greater than 10.[21]

Statistical differences were indicated if $p<0.05$ and reported p-values were two-sided. Clinically meaningful differences on the generic and disease-specific HRQL subscales were determined with Norman's 'rule of thumb', whereby a difference of »0.5 SD indicates a threshold of discriminant change in HRQL scores of a chronic illness.[22]

Based on results from our previous and ongoing studies, a standard deviation of about 20-30 points for each scale of interest (HRQL, symptoms) could be expected. Using an alpha of 0.05 and a power of 0.80, samples of respectively 100 to 250 would be necessary to detect respectively 10 to 15 points differences (considered to be clinically meaningful) between patient groups to be statistically significant. We knew beforehand that the group of LA+RT+ would be too small and the group of LA-RT- would be fairly large. However, in order to be able to include large enough numbers of LA+RT- and LA-RT+ and evaluate statistically significant differences with clinical relevance we needed to invite all stage I-II endometrial cancer survivors in our region.

Results

The 5-year overall survival rate of all 1478 women diagnosed and registered with stage I or II endometrial cancer between Jan 1, 1999 and October 1, 2007 in the region of the Eindhoven Cancer Registry was 92% among women who underwent LA vs. 88% among women who did not (p=0.004). One hospital, that did not perform routine pelvic lymph-adenectomy, declined participation in this study (N=108 patients). Among the other 9 hospitals, response rate was high, with 742 (76.9%) of the endometrial cancer survivors

returning a completed questionnaire (Figure 1). Non-respondents were older than respondents and more often underwent pelvic lymphadenectomy (Table 1). Secondary analyses according to region of treatment (e.g. 'intention to treat') revealed similar findings. In total, 457 patients were treated in the West region, and 285 patients in the East region (additional table 5).

Clinical characteristics and outcomes according to region of treatment

The rate of women receiving a systematic lymphadenectomy in the West region changed over time from 44% in 1999 to 68% in 2002, and decreased over time till 24% in 2007. In the

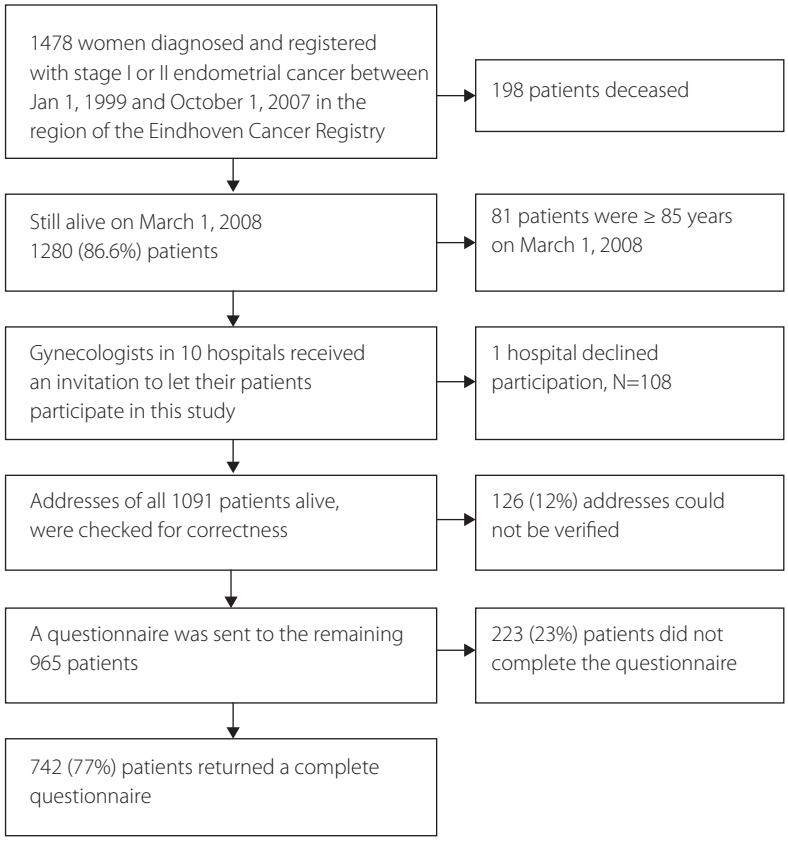

Figure 1 Flowchart selection study population.

Table 1 Sociodemographic and medical characteristics of questionnaire respondents, non-respondents and patients with unverifiable addresses diagnosed with endometrial cancer stage I-II in the period 1999-2007.

	Respondents (n=742)	Non-respondents (n=223)	Patients with unverifiable addresses (n=126)	p-value
Mean age (SD) at time of survey	66.7 (8.5)	69.4 (8.9)	66.8 (10.2)	0.0002
< 60	160 (21.6)	37 (16.6)	28 (22.2)	
≥ 60	582 (78.4)	186 (83.4)	98 (77.8)	0.25
Mean years (SD) since diagnosis	4.4 (2.4)	4.8 (2.4)	4.6 (2.3)	0.076
<2 years	152 (20.5)	30 (13.5)	20 (15.9)	
2- <5 years	286 (38.5)	93 (41.7)	49 (38.9)	
5- <10 years	304 (41.0)	100 (44.8)	57 (45.2)	0.16
FIGO stage at diagnosis				
IA	117 (15.8)	37 (16.6)	13 (10.3)	
IB	375 (50.5)	104 (46.6)	75 (59.5)	
IC	194 (26.2)	65 (29.2)	30 (23.8)	
IIA	28 (3.8)	8 (3.6)	3 (2.4)	
IIB	28 (3.8)	9 (4.1)	5 (4.0)	0.58
Histological grade				
1	350 (47.2)	99 (44.4)	57 (45.2)	
2	288 (38.8)	85 (38.1)	44 (34.9)	
3	78 (10.5)	25 (11.2)	20 (15.9)	
unknown	26 (3.5)	14 (6.3)	5 (4.0)	0.35
Primary treatment				
Surgery alone	567 (76.4)	172 (77.1)	102 (81.0)	
Surgery and radiotherapy	167 (22.5)	49 (22.0)	21 (16.7)	
Surgery and systemic	8 (1.1)	2 (0.9)	3 (2.4)	0.44
Lymphadenectomy	212 (28.6)	64 (28.7)	46 (36.5)	0.001
LA-RT-	377 (50.8)	118 (52.9)	63 (50.0)	
LA+RT-	198 (26.7)	55 (24.7)	41 (32.5)	
LA-RT+	153 (20.6)	41 (18.4)	17 (13.5)	
LA+RT+	14 (1.9)	9 (4.0)	4 (5.0)	0.16
Recurrence	21 (2.8)	10 (4.5)	5 (4.0)	0.43
Metastasis	9 (1.2)	4 (1.8)	2 (1.6)	0.79

East region lymphadenectomy was performed in 0% up to 8% of the patients over time. There were significantly more patients with grade 1 tumor in the 'East' region when compared to the West region (Table 2); more patients received adjuvant radiotherapy. One third of patients in both regions fulfilled the PORTEC criteria for adjuvant radiotherapy

Table 2 Patient demographic and clinical characteristics of respondents according to treatment received.

	LA- RT- (N=377)	LA+ RT- (N=198)	LA-RT+ (N=153)	LA+RT+ (N=14)	p-value
Mean age (SD) at time of survey	65.5 (8.9)	66.8 (8.2)	69.6 (7.4)	65.1 (8.1)	<0.0001
< 60	97 (25.7)	42 (21.2)	18 (11.8)	3 (21.4)	
≥ 60	280 (74.3)	156 (78.8)	135 (88.2)	11 (78.6)	0.006
Mean years (SD) since diagnosis	4.4 (2.4)	4.8 (2.3)	4.0 (2.6)	4.3 (2.8)	0.044
<2 years	73 (19.4)	30 (15.2)	45 (29.4)	4 (28.6)	
2- <5 years	156 (41.4)	69 (34.9)	57 (37.3)	4 (28.6)	
5- <10 years	148 (39.3)	99 (50.0)	51 (33.3)	6 (42.9)	0.007
FIGO stage at diagnosis					
IA	86 (22.8)	28 (14.1)	3 (2.0)	0 (-)	
IB	249 (66.1)	114 (57.6)	12 (7.8)	0 (-)	
IC	37 (9.8)	46 (23.2)	102 (66.7)	9 (64.3)	
IIA	3 (0.8)	5 (2.5)	19 (12.4)	1 (7.1)	
IIB	2 (0.5)	5 (2.5)	17 (11.1)	4 (28.6)	<0.0001
Histological grade					
1	226 (60.0)	50 (25.3)	71 (46.4)	3 (21.4)	
2	118 (31.3)	107 (54.0)	58 (37.9)	5 (35.7)	
3	19 (5.0)	31 (15.7)	22 (14.4)	6 (42.9)	
unknown	14 (3.7)	10 (5.1)	2 (1.3)	0 (-)	<0.0001
Systemic treatment	7 (1.9)	1 (0.5)	0 (-)	0 (-)	-
Type of radiotherapy	-	-			
Brachytherapy			35 (22.9)	0 (-)	
Brachytherapy and EBRT			17 (11.1)	4 (28.6)	
EBRT			101 (66.0)	10 (71.4)	0.041
Number of nodes harvested	-		-		
1-4		10 (5.0)		3 (21.4)	
5-9		42 (21.2)		5 (35.7)	
10-14		63 (31.8)		3 (21.4)	
>14		83 (41.9)		3 (21.4)	-
Median (range)		13 (1-42)		8 (1-19)	
# PORTEC1 criteria present in stage I disease[1]					
0	79 (21.1)	29 (15.0)	3 (2.2)	0 (-)	
1	259 (69.1)	102 (52.9)	12 (8.8)	0 (-)	
2	33 (8.8)	54 (28.0)	111 (81.6)	6 (60.0)	
3	4 (1.1)	8 (4.2)	10 (7.4)	4 (40.0)	<0.0001
2/3 PORTEC1 criteria present in stage I or stage II disease[1]	39 (10.3)	67 (33.8)	138 (90.2)	14 (100)	<0.0001
Recurrence	7 (1.9)	12 (6.1)	2 (1.3)	0 (-)	0.015
Metastasis	3 (0.8)	3 (1.5)	3 (2.0)	0 (-)	0.66

Table 2 Continued.

	LA- RT- (N=377)	LA+ RT- (N=198)	LA-RT+ (N=153)	LA+RT+ (N=14)	p-value
Co-morbidity at diagnosis					
None	152 (40.3)	78 (39.4)	57 (37.3)	5 (35.7)	
1	114 (30.2)	70 (35.4)	60 (39.2)	4 (28.6)	
2 or more	70 (18.6)	28 (14.4)	29 (19.0)	3 (21.4)	
unknown	41 (10.9)	22 (11.1)	7 (4.6)	2 (14.3)	0.31
Co-morbidity at survey					
None	97 (25.7)	49 (24.8)	31 (20.3)	4 (28.6)	
1	103 (27.3)	48 (24.2)	44 (28.9)	4 (28.6)	
2 or more	177 (47.0)	101 (51.0)	78 (51.0)	6 (42.9)	0.82
Most frequent comorbid conditions at survey					
Hypertension	151 (40.1)	86 (43.4)	71 (46.4)	4 (28.6)	0.39
Arthrosis	132 (35.0)	70 (35.4)	53 (34.6)	6 (42.9)	0.94
Heart diseases	47 (12.5)	22 (11.1)	18 (11.8)	4 (28.6)	0.29
Diabetes	41 (10.9)	24 (12.1)	13 (8.5)	2 (14.3)	0.23
Body Mass Index (self-reported at survey) [2]					
<25	119 (32.5)	64 (35.2)	44 (29.7)	5 (35.7)	
25-<30	112 (30.6)	64 (35.2)	56 (37.8)	4 (28.6)	
30-<35	75 (20.5)	36 (19.8)	33 (22.3)	4 (28.6)	
≥35	60 (16.4)	18 (9.9)	15 (10.1)	1 (7.1)	0.42
Education[3]					
Low (preliminary school)	80 (21.2)	48 (24.2)	43 (28.1)	4 (28.6)	
Medium	244 (64.7)	125 (63.1)	90 (58.8)	8 (57.1)	
High (University)	39 (10.3)	13 (6.6)	17 (11.1)	2 (14.3)	0.46
Socio-economic status					
Low	85 (22.6)	37 (18.7)	38 (24.8)	4 (28.6)	
Medium	160 (42.4)	81 (40.9)	61 (39.9)	6 (42.9)	
High	117 (31.0)	67 (33.8)	53 (34.6)	4 (28.6)	
Elderly home	10 (2.7)	11 (5.6)	1 (0.7)	0 (-)	0.39
Marital status[4]					
Married/living together	273 (74.2)	133 (71.5)	101 (66.9)	9 (64.3)	
Single/Divorced	39 (10.6)	22 (11.8)	18 (11.9)	2 (14.3)	
Widowed	56 (15.2)	31 (16.7)	32 (21.2)	3 (21.4)	0.72
Current occupation					
Unemployed	101 (26.8)	52 (26.3)	27 (17.7)	4 (28.6)	
Employed	67 (17.8)	27 (13.6)	14 (9.2)	3 (21.4)	
Retired	194 (51.5)	114 (57.6)	111 (72.6)	7 (50.0)	
Disabled/incapable of work	15 (4.0)	5 (2.5)	1 (0.7)	0 (-)	0.0005

EBRT=External Beam Radiotherapy

[1] According to PORTEC 1 trial, radiotherapy should be applied to stage I endometrial cancer when at least two of following criteria are present: tumour grade III, deep myometrial invasion (≥1/2 myometrium), age ≥ 60 years[11], [2] missing for 32 patients, [3] missing for 29 patients, [4] missing for 23 patients.

in stage I or IIA disease, or had stage IIB disease. In the West region, 45% of these patients received adjuvant RT (7.5% also lymphadenectomy) vs. 81% in the East region. In contrast, 41% of the West region underwent a lymphadenectomy. Seventeen patients (3.7%) in the West region were diagnosed with recurrent disease during follow-up compared to 4 (1.4%) in the East region. After adjustment general health, vitality and role functioning-emotional were statistically significantly, but not clinically relevantly[23] higher among women treated in the East region (Table 4). Also, women in the West region reported more symptoms regarding lymphedema, body-image and hair-loss, but these differences were again not clinically relevant.

Clinical characteristics and outcomes according to actual treatment received

No differences according to treatment were observed regarding metastasis, comorbidity, body mass index, education, socio-economic status, or marital status. The LA-RT+ group was older than the other three groups, more recently diagnosed, and more often retired. Patients in the LA+RT+ group more often received EBRT compared to patients in the LA-RT+ group. A gradient in stage and grade distribution was observed, with LA-RT- patients having the lowest stage and grade and LA+RT+ patients having the highest stage and grade. This gradient was also observed when counting the number of PORTEC1 criteria[11] for adjuvant radiotherapy in stage I disease: Only 10% of the LA-RT- patients had ≥2 criteria positive (> 50% myometrial invasion, grade 3 histological type, age ≥60 years) or stage II disease, 34% of LA+RT- patients, 90% of LA-RT+ patients and 100% of LA+RT+ patients ($p<0.0001$). Twelve of 21 recurrences were observed in the LA+RT- group ($p=0.015$). Women who received lymphadenectomy reported on average 5 points higher on the EORTC-EN24 lymphedema symptom scale (Table 3). Direct comparison between LA+RT- and LA-RT- showed statistical significance. Twenty-two percent of women who underwent lymphadenectomy reported 'quite a bit' or 'very much' 'a heavy feeling in one or both legs', compared to 13% of women without lymphadenectomy. Analyses by number of nodes harvested showed that the mean lymphedema symptoms scale score increased when more nodes were harvested (Figure 2A).

Sixteen percent of women who received adjuvant EBRT reported to have had 'quite a bit' or 'very much' diarrhea, compared to 5% of women who received no radiotherapy, and 3% of women who received brachytherapy. Gastrointestinal and diarrhea symptoms were highest among women who received EBRT (Figure 2B).

Women who were treated with adjuvant radiotherapy reported on average 6-7 points higher on the EORTC-EN24 gastrointestinal symptoms scale ($p=0.005$) and 7-10 points higher on diarrhea ($p=0.0004$) (Table 3). Excluding 35 women who only received brachytherapy resulted in somewhat worse functioning and higher symptoms scores among the radiotherapy groups, but differences were not statistically nor clinically significant. Sixteen percent of women who received adjuvant EBRT reported to have had 'quite a bit' or 'very much' diarrhea, compared to 5% of women who received no

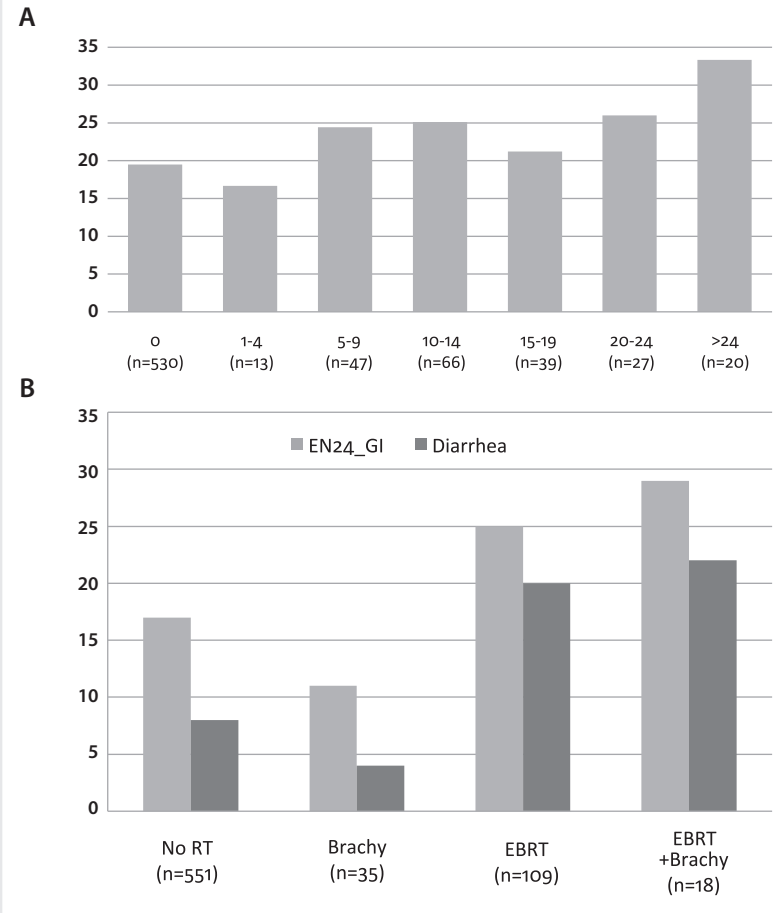

Figure 2 **A** Mean score on EN24_lymfoedema scale according to number of lymph nodes harvested. **B** Mean score on EN24_gastrointestinal scale and diarrhea according radiotherapy received

radiotherapy, and 3% of women who received brachytherapy only. Gastrointestinal and diarrhea symptoms were highest among women who received EBRT (Figure 2B).

Patients who survived a locoregional recurrence (n=21) reported lower HRQL scores on almost all SF36 subscales, but this was only statistically significant and clinically relevantly

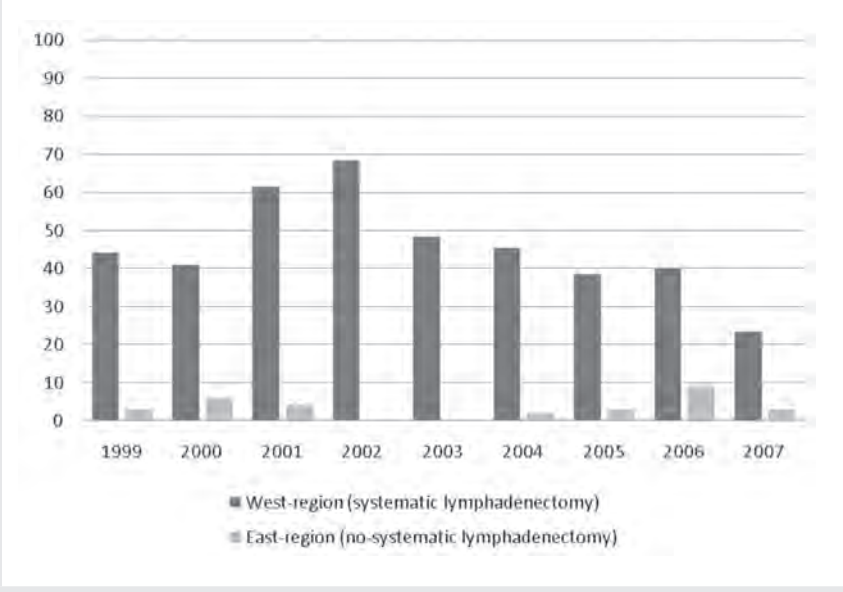

Figure 3 Percentage of women receiving lymphadenectomy per year according to region of treatment.

lower for role functioning physical (Table 3). They also reported more problems with taste change and less sexual interest. Seventeen patients (3.7%) in the West region were diagnosed with recurrent disease during follow-up compared to 4 (1.4%) in the East region. This difference did not reach statistical significance (p=0.06). After adjustment, general health, vitality and role functioning-emotional were statistically, but not clinically[23] significantly better among women treated in the East region (additional table 6).

Multivariate linear regression analyses evaluating the association between patient and treatment characteristics with HRQL and symptoms

Age, BMI and comorbidity were the most important predictors for many HRQL scales as well as symptoms scales (Table 4). Years since diagnosis and stage were not associated with symptoms or HRQL and therefore not reported in the table. Lymphadenectomy and radiotherapy were associated with lymphedema symptoms and gastrointestinal symptoms and diarrhea respectively. To ensure that the multivariate analysis results were not influenced by the strong association between HRQL and metastasis or recurrence, we performed secondary analyses with only disease-free survivors. These results were comparable to those using the full sample (data not shown).

Table 3 Analysis of (co-)variance of outcome variables according to lymphadenectomy and/or radiotherapy received or recurrence

	LA- RT- (N=377)	LA+ RT- (N=198)	LA-RT+ (N=153)	LA+RT+ (N=14)			Recurrence (n=21)	
Variable	**Mean (standard deviation)**				**P (crude)**	**P (adjusted)[1]**	**Mean (SD)**	**P (adjusted)[1]**
SF36								
Physical functioning	70 (27)	69 (30)	69 (27)	68 (31)	0.99	0.29	61 (33)	0.95
Role functioning physical	70 (40)	69 (42)	62 (44)	67 (39)	0.36	0.76	*42 (48)*	*0.049*
Bodily pain	74 (24)	73 (25)	74 (26)	70 (29)	0.92	0.79	70 (28)	0.91
General health	66 (21)	65 (21)	63 (20)	58 (18)	0.40	0.69	54 (26)	0.10
Vitality	65 (20)	65 (21)	65 (20)	62 (23)	0.93	0.92	60 (20)	0.63
Social functioning	81 (25)	83 (24)	80 (23)	72 (31)	0.42	0.32	73 (28)	0.78
Role functioning emotional	82 (35)	82 (36)	82 (34)	85 (38)	0.99	0.53	65 (44)	0.14
Mental health	75 (18)	77 (17)	76 (17)	77 (16)	0.84	0.86	75 (17)	0.95
EORTC-EN24								
Lymphedema	20 (26)	*25 (27)*[2]	19 (24)	25 (30)	0.12	0.10	29 (30)	0.17
Urological symptoms	23 (22)	25 (23)	24 (21)	23 (22)	0.71	0.54	33 (24)	0.19
Gastrointestinal symptoms	*16 (17)*	*17 (18)*	*23 (21)*[3]	*23 (20)*	*0.005*	0.17	20 (24)	0.95
Diarrhea[4]	*10 (21)*	*7 (20)*	*17 (28)*	*13 (29)*	*0.0004*	*0.0002*	17 (35)	0.56
Body image problems	9 (19)	8 (18)	6 (14)	8 (27)	0.44	0.77	10 (19)	0.89
Sexual/vaginal problems[5]	25 (28)	32 (30)	26 (26)	24 (24)	0.44	0.65	-	-
Back/pelvic pain	26 (30)	27 (29)	25 (30)	13 (26)	0.43	0.51	23 (22)	0.45
Tingling/numbness	21 (28)	19 (27)	14 (23)	24 (33)	0.11	0.49	18 (23)	0.86
Muscular/joint pain	33 (30)	35 (30)	31 (27)	31 (28)	0.59	0.85	25 (22)	0.22
Hair loss	9 (21)	9 (19)	7 (18)	14 (25)	0.37	0.26	12 (25)	0.28
Taste change	3 (13)	4 (17)	4 (13)	10 (28)	0.43	0.49	*12 (28)*	*0.02*
Sexual Interest	16 (20)	17 (22)	13 (18)	23 (25)	0.20	0.30	4 (12)	0.06
Sexual activity	17 (21)	17 (20)	14 (18)	21 (22)	0.43	0.59	16 (6)	0.80
Sexual enjoyment[5]	43 (29)	43 (27)	40 (25)	47 (33)	0.87	0.53	-	-

[1] adjusted for age at survey, stage of cancer, grade of cancer, years since diagnosis, marital status, BMI, education, socio-economic status, co-morbidity, [2] Direct comparison between LA+RT- and LA-RT- resulted in a crude p-value of 0.05 and an adjusted p-value of 0.04, [3] Direct comparison between LA-RT+ and LA-RT- resulted in a crude p-value of 0.0006 and an adjusted p-value of 0.04, [4] additional EORTC QLQ-C30 item was added as diarrhea was not assessed in the SF36 or EN24, [5] Calculated only for women who reported to be sexually active in past 4 weeks (n=132 (35%) for LA-RT-, n=76 (38%) for LA+RT-, n=50 (33%) for LA-RT+ and n=7 (50%) for LA+RT+), Only 2 women with a recurrence completed these items.

Table 4 Standardized betas of multivariate linear regression analyses evaluating the association of independent variables with the SF-36 and EORTC-QLQ-EN24 subscales, all patients combined

	N	Age	Grade	LA	RT	recur	meta	BMI	comorb	SES	educ	Married
SF36												
Physical functioning	672	-1.0***					-27.1**	-1.2***	-11.3		-5.6*	5.6**
Role functioning physical	651	-0.8***					-30.0*	-0.7*	-15.8***			
Bodily pain	694	-0.3*						-0.6***	-14.4***			
General health	669						-21.1*		-12.5***			
Vitality	691						-18.3*	-0.5***	-10.8***			4.8**
Social functioning	709								-6.1**	-5.0*		6.7**
Role functioning emotional	645	-0.4*						-0.6*	-8.8**			6.9*
Mental health	687								-7.7***		-5.2**	3.9*
EORTC-EN24												
Lymphedema	685	0.3*		5.9*				1.0***	5.3*			-5.0*
Urological symptoms	689	0.3**						0.3*	6.6**			-4.4*
Gastrointestinal symptoms	687				4.9*				6.2**			
Diarrhea	677				8.0**				5.1*		5.7**	
Body image problems	689	-0.3**							4.4**			
Sexual/vaginal problems	260	-0.8**				56.1**		-1.3***				
Back/pelvic pain	677							0.4*	14.1***			
Tingling/numbness	686							0.4*	7.6**			
Muscular/joint pain	687	0.4*						0.4*	16.8***			
Hair loss	686	0.2*					19.3*					
Taste change	688						19.4**					
Sexual Interest	650	-0.4**	5.2*			-11.2*	-14.7*				-4.5*	7.4***
Sexual activity	652	-0.4**										13.1***
Sexual enjoyment	255		17.3**								-19.2***	

N=number of observations in model, LA=Lymphadenectomy, RT=Radiotherapy, recur=recurrence, meta=metastasis, BMI=body mass index, comorb=comorbid conditions; SES=Socio-economic status, educ=education

Age and BMI were included as continuous variables, tumor grade: 3 vs. 1,2; LA: yes vs. no, RT: yes vs. no, recurrence: yes vs. no; metastasis: yes vs no, co-morbidity: yes vs. no; low SES vs medium and high, low education vs. medium and high, married vs. not married; Years since diagnosis (continuous) and tumor stage: 1C, 2A,2B vs. 1A,1B were not associated with symptoms or health status and therefore not shown;

***$p<0.0001$; **$p<0.01$; *$p<0.05$

Table 5 Patient demographic and clinical characteristics of respondents according to region of diagnosis and treatment.

	West-region (systematic lymphadenectomy) (N=457)	East-region (no-systematic lymphadenectomy (N=285)	p-value
Mean age (SD) at time of survey	66.7 (8.8)	66.7 (8.2)	0.98
< 60	100 (21.9)	60 (21.1)	
≥ 60	357 (78.1)	225 (79.0)	0.79
Mean years (SD) since diagnosis	4.5 (2.5)	4.3 (2.4)	0.17
<2 years	86 (18.8)	66 (23.2)	
2- <5 years	172 (37.6)	114 (40.0)	
5- <10 years	199 (43.5)	105 (36.8)	0.15
FIGO stage at diagnosis			
IA	67 (14.7)	50 (17.5)	
IB	244 (53.4)	131 (46.0)	
IC	114 (25.0)	80 (28.1)	
IIA	17 (3.7)	11 (3.9)	
IIB	15 (3.3)	13 (4.6)	0.37
Histological grade			
1	176 (38.5)	174 (61.1)	
2	203 (44.4)	85 (29.8)	
3	58 (12.7)	20 (7.0)	
unknown	20 (4.4)	6 (2.1)	<0.0001
Primary treatment			
Surgery alone	371 (81.2)	196 (68.8)	
Surgery and radiotherapy (RT)	80 (17.5)	87 (30.5)	
Surgery and systemic	6 (1.3)	2 (0.7)	0.0002
Type of radiotherapy			
Brachy	10 (12.5)	25 (28.7)	
Brachy and EBRT	11 (13.8)	10 (11.5)	
EBRT	59 (73.8)	52 (59.8)	0.04
Lymphadenectomy (LA)	205 (44.9)	7 (2.5)	<0.0001
Number of nodes harvested			
1-4	11	2	
5-9	45	2	
10-14	65	1	
>14	84	2	
Median (range)	13 (1-42)	8 (1-24)	
# PORTEC1 criteria present in stage I or IIA disease[1]			
0	72 (16.3)	39 (14.3)	
1	224 (50.7)	149 (54.8)	
2	127 (28.2)	77 (28.3)	
3	19 (4.3)	7 (2.8)	0.50
2/3 PORTEC1 criteria present in stage I or IIA disease or stage IIB disease[1]	161 (35.2)	97 (34.0)	0.82
LA – RT -	22 (13.7)	17 (17.5)	
LA + RT -	66 (41.0)	1 (1.0)	
LA - RT +	61 (37.9)	77 (79.4)	
LA + RT +	12 (7.5)	2 (2.1)	<0.0001
Recurrence	17 (3.7)	4 (1.4)	0.06
Metastasis	6 (1.3)	3 (1.1)	0.75

Table 5 Continued

	West-region (systematic lymphadenectomy) (N=457)	East-region (no-systematic lymphadenectomy (N=285)	p-value
Co-morbidity at diagnosis			
None	173 (37.9)	119 (41.8)	
1	161 (35.2)	87 (30.5)	
2 or more	80 (17.5)	50 (17.5)	
unknown	43 (9.4)	29 (10.2)	0.58
Co-morbidity at survey			
None	112 (24.5)	69 (24.2)	
1	113 (24.7)	86 (30.2)	
2 or more	232 (50.8)	130 (45.6)	0.23
Most frequent comorbid conditions at survey			
Hypertension	194 (42.5)	118 (41.4)	0.78
Arthrosis	164 (35.9)	97 (34.0)	0.71
Heart diseases	55 (12.0)	36 (12.6)	0.81
Diabetes	49 (10.7)	31 (10.9)	0.94
Body Mass Index (self-reported at survey) [2]			
<25	145 (31.7)	87 (30.5)	
25-<30	139 (30.4)	97 (34.0)	
30-<35	93 (20.4)	55 (19.3)	
≥35	54 (11.8)	40 (14.0)	0.14
Education[3]			
Low (preliminary school)	113 (24.7)	62 (21.8)	
Medium	283 (61.9)	184 (64.6)	
High (University)	39 (8.5)	32 (11.2)	0.20
Socio-economic status			
Low	102 (22.3)	62 (21.8)	
Medium	189 (41.4)	119 (41.8)	
High	144 (31.5)	97 (34.0)	
Elderly home	17 (3.7)	5 (1.8)	0.57
Marital status[4]			
Married/living together	307 (67.2)	209 (73.3)	
Single/Divorced	55 (12.0)	26 (9.1)	
Widowed	75 (16.4)	47 (16.5)	0.04
Current occupation			
Unemployed	121 (26.5)	63 (22.1)	
Employed	65 (14.2)	46 (16.1)	
Retired	256 (56.0)	170 (59.7)	
Disabled/incapable of work	15 (3.3)	6 (2.1)	0.38

EBRT=External Beam Radiotherapy

[1] According to PORTEC 1 trial, radiotherapy should be applied to stage I or stage IIA cancer when at least two of following criteria are present: tumour grade III, deep myometrial invasion (≥1/2 myometrium), age ≥ 60 years[11], [2] missing for 32 patients, [3] missing for 29 patients, [4] missing for 23 patients

Table 6 Analysis of covariance of outcome variables for patients treated in 'routine lymphadenectomy care' and 'no-routine lymphadenectomy care' hospitals

	West-region (systematic LA) (N=457)	East-region (no-systematic LA) (N=285)		
Variable	**Mean scores (SD)**		**P (crude)**	**P (adjusted)[1]**
SF36				
Physical functioning	68 (29)	71 (26)	0.13	0.25
Role functioning physical	66 (42)	72 (39)	0.06	0.10
Bodily pain	72 (25)	77 (24)	0.02	0.06
General health	64 (21)	67 (21)	0.04	0.05
Vitality	63 (20)	68 (19)	0.004	0.003
Social functioning	80 (25)	83 (24)	0.21	0.34
Role functioning emotional	80 (37)	86 (32)	0.02	0.03
Mental health	75 (17)	77 (18)	0.28	0.29
EORTC-EN24				
Lymphedema	23 (27)	17 (24)	0.002	0.007
Urological symptoms	25 (23)	22 (21)	0.11	0.20
Gastrointestinal symptoms	19 (19)	17 (18)	0.39	0.70
Diarrhea[2]	10 (22)	12 (23)	0.20	0.10
Body image problems	10 (20)	6 (14)	0.01	0.009
Sexual/vaginal problems[3]	29 (28)	25 (28)	0.26	0.61
Back/pelvic pain	28 (30)	23 (28)	0.03	0.11
Tingling/numbness	20 (27)	18 (26)	0.32	0.40
Muscular/joint pain	35 (30)	30 (28)	0.02	0.07
Hair loss	10 (21)	7 (17)	0.02	0.02
Taste change	4 (16)	3 (12)	0.49	0.58
Sexual Interest	16 (20)	16 (20)	0.94	0.72
Sexual activity	16 (20)	17 (21)	0.45	0.91
Sexual enjoyment[3]	44 (27)	42 (28)	0.55	0.26

[1] adjusted for age at survey, stage of cancer, grade of cancer, marital status, BMI, education, socio-economic status, co-morbidity.

[2] additional EORTC QLQ-C30 item was added as diarrhea was not assessed in the SF36 or EN24

[3] Calculated only for women who reported to be sexually active in past 4 weeks (n=158 (42%) in West-region and 106 (45%) in East-region)

Discussion

This population-based analysis revealed distinct symptom patterns in early stage endometrial cancer survivors who received different treatment strategies: routine pelvic lymphadenectomy without RT in the presence of risk factors compared to no lymphadenectomy and adjuvant radiotherapy according to the PROTEC criteria. However, these differences did not result in clinically relevant differences in HRQL between the different groups. Our hypothesis that women undergoing pelvic lymphadenectomy – to try to avoid radiotherapy- would overall report a better HRQL compared to women who did not, but were administered EBRT in the presence of risk factors is therefore rejected. Observed differences in overall survival between women receiving LA and those who did not have been observed in a previous study in our region[12] and can be postulated to be explained by other confounding factors, such as lower BMI, and younger age among women receiving LA.

In a previous study in our West region, including 335 women with endometrial cancer stage I diagnosed between 1998 and 2004, 237 women received pelvic lymphadenectomy.[11] It was concluded that in stage I patients without risk-factors, lymphadenectomy could be omitted. After that the proportion of women who received lymphadenectomy slowly decreased.

Lymphedema symptoms score was related to the number of resected lymph nodes. This is in line with a large retrospective chart review including 670 patients who underwent a lymphadenectomy at initial surgery; symptomatic lymphedema was limited to patients with > 10 removed lymph nodes.[10] Yet the incidence in this chart review of lymphedema was only 2,4% which may be an underestimation since women who have lymphedema complaints, without clinically confirmed lymphedema will not be identified in a chart review. In the ASTEC trial, the incidence of lymphedema in the lymphadenectomy group was substantially increased compared to standard surgery, although clinicians may not have reported milder cases, since all reported cases of lymphedema were moderate and severe.[5] The Italian trial also reported more frequent postoperative complications among patients who received lymphadenectomy, which was mostly due to lymphedema.[4] We strongly believe it would be very interesting to evaluate quality of life and symptoms among ASTEC or Italian trial participants during follow-up, as was recently done for the long-term PORTEC-1 survivors.[8] Despite the lack of a baseline measurement, due to the randomised nature of both trials, it can be expected that the influence of selection bias on patient reported outcomes will be minimal.

Women in our study who underwent lymphadenectomy without radiotherapy, more often had a recurrence during follow-up compared to the patients without lymphadenectomy. This is in accordance with previous observations.[8,23] Women who survived a recurrence, reported lower HRQL scores on almost all subscales, which was only statistically significant and clinically relevant lower for physical role functioning. As this was a very

small group, sensitivity analyses revealed no important impact on the outcomes per treatment group.

Patients having external beam radiotherapy reported higher gastrointestinal symptom burden than women receiving only brachytherapy, which is comparable to quality of life outcomes of the PORTEC-2 trial.[7]

The present study has limitations that should be mentioned. We invited only patients that were diagnosed with FIGO stage I or stage II disease to complete a questionnaire, thereby excluding patients that were diagnosed with FIGO stage IIIC solely based on the presence of pelvic lymph-node metastases. Based on a previous study in our region[12] we expect that about five percent of women who underwent lymphadenectomy had been diagnosed with FIGO stage IIIC. In our study this has probably resulted in the exclusion of about 10 patients the LA+RT+ group. As the LA+RT+ cohort reported highest symptoms scores, we may have underestimated the symptoms scores and overestimated the HRQL of patients in this group. We do not expect that the exclusion of this small number of patients may have changed our results; on the contrary, it inclusion of this group would have strengthened the findings.

Although information was available on the characteristics of non-respondents and patients with unverifiable addresses, it remains unknown whether non-respondents declined to participate in the study because of poor health.

Inclusion of long-term survivors could introduce also survival bias into our sample selection, but this might not be a problem as there was a lack of association between years since diagnosis and HRQL. This persistence of symptoms related to radiotherapy has also been observed in the long-term PORTEC-1 outcomes.[8]

Furthermore, our cross-sectional analysis limits the determination of causal association between treatment and HRQL as baseline data on these patient-reported outcomes are unknown. Finally, possible confounding by indication could be present as treatment is linked to cancer stage and grade.

Despite the limitations, the present study provides an important contribution to the data on the impact of routine lymphadenectomy or adjuvant radiotherapy on the HRQL and symptom experience of early stage endometrial cancer survivors. These results call for further research on the effect of pelvic lymphadenectomy among cancer survivors followed over a longer period of time, and we expect that the large prospective trial assessing the incidence of lower extremity lymphedema that is currently being developed by the GOG will provide some answers.[3] Recent results from a prospective multicentre study suggest that sentinel lymph-node biopsy could be a trade-off between systematic lymphadenectomy and no lymphadenectomy at all in patients with low risk endometrial cancer, tailoring adjuvant therapy without increased morbidity.[24]

In conclusion, women receiving pelvic lymphadenectomy reported no clinically relevant better HRQL or fewer symptoms compared to women who received radiotherapy or no adjuvant treatment at all. Using lymphadenectomy to tailor external beam radiotherapy

and prevent over-treatment in low-risk clinical early stage patients can therefore be debated. Especially since PORTEC-2[7,14] publications will lead to increased use of brachytherapy and thus even less gastrointestinal symptoms in patients who receive RT when additional risk factors are found after surgery. In addition to the fact that there is no evidence that pelvic lymphadenectomy decreases the risk of death or disease recurrence, pelvic lymphadenectomy cannot be recommended for stage I-II endometrial cancer.

Raw data from this study will be made available for non-commercial scientific research, subject to study question, privacy and confidentiality restrictions, and registration and can be obtained via our website: www.profilesregistry.nl[25]

References

1. Netherlands Cancer Registry, 1989-2010, www.kankerregistratie.nl based on April 2011 NCR data submission, posted to the NCR web site 2011
2. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2008, http://seer.cancer.gov/csr/1975_2008/ based on November 2010 SEER data submission, posted to the SEER web site, National Cancer Institute. Bethesda, MD, 2011
3. Leitao MM, Barakat RR: Advances in the management of endometrial carcinoma. Gynecol Oncol 120:489-92
4. Benedetti Panici P, Basile S, Maneschi F, et al: Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 100:1707-16, 2008
5. Kitchener H, Swart AM, Qian Q, et al: Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373:125-36, 2009
6. May K, Bryant A, Dickinson HO, et al: Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev:CD007585
7. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al: Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 27:3547-56, 2009
8. Nout RA, van de Poll-Franse LV, Lybeert ML, et al: Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol 29:1692-700
9. van de Poll-Franse LV, Mols F, Essink-Bot ML, et al: Impact of external beam adjuvant radiotherapy on health-related quality of life for long-term survivors of endometrial adenocarcinoma: a population-based study. Int J Radiat Oncol Biol Phys 69:125-32, 2007
10. Abu-Rustum NR, Alektiar K, Iasonos A, et al: The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. Gynecol Oncol 103:714-8, 2006
11. Creutzberg CL, van Putten WL, Koper PC, et al: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 355:1404-11, 2000
12. Zuurendonk LD, Smit RA, Mol BW, et al: Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. Eur J Surg Oncol 32:450-4, 2006
13. Janssen-Heijnen MLG, Louwman WJ, Van de Poll-Franse LV, et al: Results of 50 years cancer registry in the South of the Netherlands: 1955-2004 (in Dutch). Eindhoven, Eindhoven Cancer Registry, 2005
14. Nout RA, Smit VT, Putter H, et al: Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 375:816-23
15. UICC: TNM Atlas Illustrated Guide to the TNM/pTNM Classification of Malignant Tumors, 4th edn, 2nd Revision ed. Berlin, Springer-Verlag, 1992, pp 141-144
16. Sangha O, Stucki G, Liang MH, et al: The self-administered comorbidity questionnaire: A new method to assess comorbidity for clinical and health services research. Arthritis Rheum 49:156-163, 2003
17. van Duijn C, Keij I: Sociaal-economische status indicator op postcode niveau. Maandstatistiek van de bevolking 50:32-5, 2002
18. Aaronson NK, Muller M, Cohen PD, et al: Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 51:1055-68, 1998
19. Greimel E, Nordin A, Lanceley A, et al: Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 47:183-90
20. Babyak MA: What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 66:411-21, 2004
21. Kleinbaum DG, Kupper LL, Muller KE, et al: Applied regression analysis and other multivariable methods (3rd ed). California, Brooks/Cole Publishing Company, 1998
22. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41:582-92, 2003

23. Blake P, Swart AM, Orton J, et al: Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 373:137-46, 2009
24. Ballester M, Dubernard G, Lecuru F, et al: Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 12:469-76
25. van de Poll-Franse LV, Horevoorts N, Eenbergen MV, et al: The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: Scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer

4.2

The relationship of Body Mass Index with quality of life among endometrial cancer survivors: a study from the population-based PROFILES registry

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Abstract

Objective

The aim of this study was to assess the association of Body Mass Index (BMI) and Health-Related Quality of Life (HRQoL), and the relative importance of BMI in explaining variation in QoL among stage I or II endometrial cancer (EC), independent of comorbidities, socio-demographic and clinical characteristics.

Methods

A population-based, cross-sectional survey conducted in 2008 among endometrial cancer survivors diagnosed between 1999 and 2007 sampled from the Eindhoven Cancer Registry. The HRQoL (SF-36), EC specific HRQoL (EORTC-QLQ-EN24), comorbidities (SCQ) and fatigue (FAS) questionnaire were completed by 666 endometrioid EC survivors. Multivariate regression analyses were used to assess the associations of HRQoL with BMI reported at time of questionnaire completion and to assess the percentage of variance in HRQoL outcomes explained by BMI (R^2), (controlled for socio-demographic and clinical characteristics and comorbidity).

Results

Of all women, 432 (67,6%) were pre-obese (BMI 25-30) or obese (BMI >30). Increased BMI was associated with decreased physical function, decreased vitality, more lymphoedema symptoms, decreased sexual/vaginal problems, less taste change and more fatigue symptoms. BMI added significantly to the explained variance of physical function (4.3%), physical limitations in daily life (role physical; 0.7%), bodily pain (1.5%), vitality (1.6%), emotional limitations in daily life (role emotional; 0,9%), lymphoedema symptoms (5.2%), sexual/vaginal problems (3.2%), urologic problems (0.7%), and fatigue (1.4%).

Conclusion

BMI was related to several HRQoL outcomes. Therefore BMI needs to be taken into account in HRQoL studies. Moreover, future research should assess if interventions to decrease BMI in obese EC survivors might improve HRQoL.

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy with approximately 142,200 new cases diagnosed per year in developed countries [1]. The incidence of EC is still rising, among others due to an aging population and an increase in Body Mass Index (BMI). Currently, 39% of all EC cases is attributed to obesity in industrialized countries [2]. Overall, 85% of EC cases is discovered in an early-stage. These early stage EC patients have a good prognosis since the 5 years survival rate of stage I is approximately 75-90% [3]. The rising incidence, combined with the good prognosis of EC survivors will lead to a considerable group of long-term EC survivors whereby HRQoL and the factors which influence the HRQoL become very important.

Health-Related Quality of Life (HRQoL) of EC survivors is negatively affected by BMI, both in the general population and in EC survivors [4-6]. Overweight or obese EC survivors report a poorer general health, more fatigue symptoms, lower physical functioning, more bodily pain, and more problems with work or daily activities [7, 8]. HRQoL is also affected by the presence of comorbidities. Comorbidities are highly prevalent in EC survivors. About 70% of EC survivors report at least one comorbidity [9], while on average EC patients report 2.4 comorbidities [10]. The studies about the association between HRQoL and BMI do not include specific items for QoL in patients with endometrial cancer and need replication in a larger sample. Better understanding of the impact of BMI on HRQoL is needed to develop interventions to improve the HRQoL of the growing group endometrial cancer survivors. Because of the important association between comorbidities and HRQoL, comorbidities need to be taken into account in such a study.

Therefore, the aim of this study was (1) to assess the association between BMI and HRQoL and (2) to evaluate the amount of variance of HRQoL explained by BMI in addition to comorbidities and socio-demographic and clinical characteristics in stage I or II EC survivors. We hypothesize that BMI is associated with and adds to the explained variance of specific HRQoL outcomes in EC survivors independent of comorbidities and socio-demographic and clinical characteristics.

Methods

Setting and participants

A population-based cross-sectional survey was conducted in 2008. In total 1478 patients who were newly diagnosed with FIGO stage I or II EC in the south of The Netherlands between 1998 and 2007, were registered by the Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Center South (CCCS) that covers about 10 community hospitals.

Of these patients, 198 were deceased, 81 were 85 years old or older and excluded, 108 were from a hospital that declined participation and 126 addresses could not be verified. As a result, 965 EC survivors were invited for participation and 742 women (77%) completed the questionnaire. Patients with non-endometrioid subtypes and who received chemotherapy were excluded from the analysis. Therefore, the study population consist of 666 endometrial survivors (Figure 1). The Medical Ethics Committee of the Maxima Medical Center approved this study.

Data collection

Trained registration clerks of the ECR actively collect data on demographics, tumor and treatment information from hospital medical records. Patient reported outcomes were obtained by questionnaires through PROFILES (Patient Reported Outcomes Following Initial Treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data of the ECR. Data from the Profiles registry will be available for non-commercial scientific research, subject to study question, privacy and confidentially restrictions, and registration (http://www.profilesregistry.nl) [11].

A letter to inform about the study and the questionnaire was sent to EC survivors by their attending gynecologist. When completing the questionnaire respondents signed an informed consent form to approve linking the questionnaire to the patient specific data of the ECR. Non-respondents were sent a reminder letter and questionnaire within two months. More details have been previously published [12, 13].

Measures

Clinical and treatment information (i.e. date of birth, date of diagnosis, stage of disease and treatment related aspects) were registered in the ECR. Questionnaires assessed the weight, height, marital status, education level, comorbidities, general and endometrium-specific HRQoL and fatigue outcomes of the survivors. BMI was calculated(weight (kg)/height $(m)^2$) and categorized according to standard guidelines; normal weight (BMI <25), pre-obese (BMI 25-<30), obese class I (BMI 30-<35) and obese class II (BMI ≥35) [14]. Socio-economic status was determined by zip/postal code [15]. Comorbidity was assessed with the validated Self-administered Comorbidity Questionnaire (SCQ) [16]. Patients were asked to identify comorbid conditions present in the past 12 months. The adapted SCQ lists 14 medical conditions (with the option to list up to 3 additional conditions).

General HRQoL was measured with the Dutch version of the validated SF-36. Scales on this questionnaire include: physical functioning, role physical (problems with work or other daily activities as a result of physical health), bodily pain, general health, vitality, social

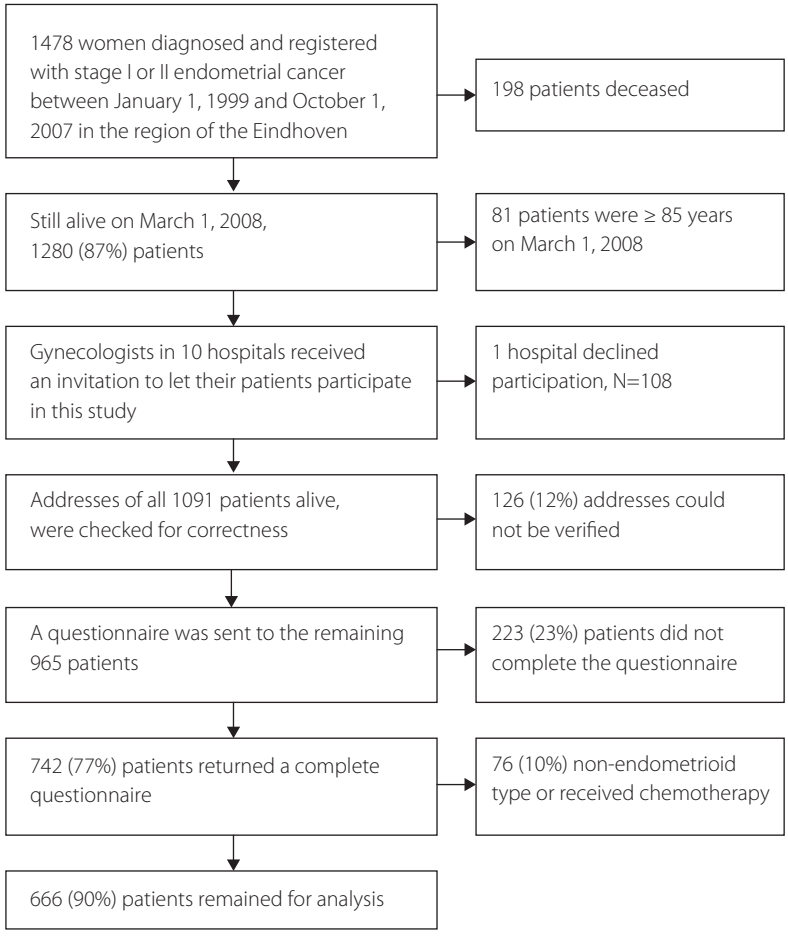

Figure 1 Flow-chart of the data collection process .

functioning, role emotional (problems with work or other daily activities as a result of emotional problems), and mental health. Scores on the 36 items were transformed into a scale from 0 to 100, where 100 denotes the best HRQoL [17].

Disease and treatment specific aspects of HRQoL of EC survivors were measured with the Dutch validated European Organization for Research and Treatment of cancer - Quality of

Life Questionnaire – Endometrial Cancer Module (EORTC-QLQ-EN24).The 24-item questionnaire comprises of 13 domains: lymphoedema, urologic problems, gastro-intestinal problems, body image, sexual/vaginal problems, back/pelvic pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity and sexual enjoyment. All items were rated on a 4-point scale from 1 (''not at all'') to 4 (''very much''). Scores were transformed into a scale from 0 to 100 where higher scores indicate more symptoms, with the exception of the latter three sex-related questions, where higher scores represent higher levels of functioning [18].

Level of fatigue was evaluated with the validated Fatigue Assessment Scale (FAS), a 10-item questionnaire. Response categories were on a 5-point scale (1 "never" to 5 "always"). Total scores can range from 10 to 50, with higher scores indicating more fatigue symptoms [19].

Statistical analyses

For the descriptives, continuous variables were represented by means and standard deviations and categorical variables by frequencies and percentages. Differences in socio-demographic and clinical characteristics (dependent variables) between respondents, non-respondents and patients with unverifiable addresses were compared using ANOVA for continuous variables and chi-square test for categorical variables. Similar analyses were used to determine differences in HRQoL and fatigue outcomes between patients in the four BMI categories.

Hierarchical multiple linear regression analyses were conducted to evaluate the relationship between patient reported outcomes (subscales of the SF-36 and EORTC-QLQ-EN24; FAS) as the dependent variables and the independent variables that were entered stepwise to the model: BMI (step 1); plus socio-demographic- and clinical characteristics (age, years since diagnose, treatment (treatment alone, treatment and adjuvant therapy and lymphadenectomy), marital status and education level) (step 2); plus number of comorbidities (step 3)). Variables entered in the regression models were determined a priori based on literature. By performing this hierarchical regression it was possible to determine the association of BMI with patient reported outcomes without adjustment (crude), when adjusting for socio-demographic and clinical characteristics and then assess if this association remained present when the number of comorbidities were entered into the model.

To assess how much of the variation in the patient reported outcomes could be explained by BMI and specific comorbidities, again hierarchical linear regression analyses were preformed. Comorbidities strongest related to patient reported outcomes (heart disease, depression, osteoarthritis and backache) and the rest category with all other comorbidities (hypertension, diabetes, rheumatism, long disease (asthma, chronic bronchitis, COPD), thyroid disease, stroke, stomach ulcer, renal disease, anemie or blood disease and, liver

disease) were stepwise used as independent variables. Explained variance (R^2) was reported for (1) socio-demographic and clinical characteristics (age, years since diagnose, treatment, marital status, education level (2) comorbidities (heart disease, depression, osteoarthritis, backache and other co-morbidities) and (3) BMI. All analyses were performed using Statistical Analysis System (SAS) version 9.2 (SAS Institute, Cary, NC, 1999). P-values were regarded as significant if $p < .05$ and tests were two-sided.

Results

Socio-demographic and clinical characteristics

Table 1 represents the socio-demographic and clinical characteristics of respondents, non-respondents and patients with unverifiable addresses. Respondents were younger than non-respondents (66.8 vs. 69.2 years) and were more likely to have a high socio-economic status (33% vs. 28%). Almost all women (92%) were aged above 55 years. The mean time since diagnosis was 4.3 years (range 0.6-9.1) and was shorter for respondents than for non-respondents. Most patients (92%) had stage I endometrial cancer at diagnosis. All survivors were post treatment and had undergone surgery. About three quarter of the survivors received surgery alone and approximately one quarter received radiotherapy. The majority of participants (68%) was either pre-obese (34%) or obese (34%). BMI values ranged from 17.7 to 58.5 with a mean BMI of 28.5.

Normal weight (BMI <25) and obese class 2 (BMI ≥35) patients were younger than pre-obese (BMI 25-<30) and obese class 1 (BMI 30-<35) patients (Table 2). Obese class 1 patients less often had a partner compared to the patients in other BMI categories. Higher BMI category was associated with lower educational level. Patients in higher BMI categories reported more comorbidities. A positive association was observed between increasing BMI category and the following comorbid conditions: hypertension, osteoarthritis, backache, diabetes, and lung disease (asthma, chronic bronchitis, COPD).

Quality of life

Mean scores of patient reported outcomes (subscales of the SF-36, EORTC-QLQ-EN24, and FAS) are described for all patients and per BMI category in table 3. Univariate linear regression analyses (crude) showed that higher levels of BMI were associated with lower levels of HRQoL according to all subscales of the SF-36, with exception of the general health and mental health scale (Table 4). After controlling for socio-demographic- and clinical characteristics and number of comorbidities, physical function and vitality remained significantly associated with BMI. A 10 point higher BMI score resulted in a decline of 8.3 points on the physical function scale and a 3.2 points decrease of vitality, both on a scale from 0-100.

Table 1 Socio-demographic and clinical characteristics of respondents, non-respondents and patients with unverifiable addresses

	Respondents (n=666)		Non-respondents (n=199)		Patients with unverifiable addresses (n=113)		p-value*
Variable	N(%)						
Age (mean, sd)	66.8	(8.5)	69.2	(8.9)	66.9	(9.4)	.003
<55	50	(8%)	8	(4%)	9	(8%)	
55-69	369	(55%)	97	(49%)	68	(60%)	
≥ 70	247	(37%)	94	(47%)	36	(32%)	.033
Years since diagnose (mean, sd)	4.3	2.4	4.9	(2.4)	4.6	(2.3)	.015
<2 years	144	(22%)	24	(12%)	19	(17%)	
2-<5 years	261	(39%)	86	(43%)	42	(42%)	
≥ 5 years	261	(39%)	89	(45%)	52	(52%)	.034
FIGO stage at diagnose							
I	615	(92%)	185	(93%)	107	(95%)	
II	51	(8%)	14	(7%)	6	(5%)	.667
FIGO stage at diagnose							
I	615	(92%)	185	(93%)	107	(95%)	
II	51	(8%)	14	(7%)	6	(5%)	.667
Grade							
1	319	(49%)	94	(50%)	55	(50%)	
2	256	(40%)	76	(40%)	41	(37%)	
3	72	(11%)	19	(10%)	15	(14%)	.915
Primary treatment							
Surgery alone	512	(77%)	154	(77%)	96	(85%)	
Surgery and radiotherapy	154	(23%)	45	(23%)	17	(15%)	.156
Socio-economic status							
Low	145	(22%)	53	(27%)	40	(36%)	
Medium	275	(42%)	81	(42%)	44	(39%)	
High	219	(33%)	55	(28%)	27	(24%)	
Elderly home	20	(3%)	5	(3%)	1	(1%)	.043

* P-values report comparison between respondents, non-respondents and patients with unverifiable addresses according to ANOVA and chi-square tests

Table 2 Socio-demographic and clinical characteristics of respondents according to BMI category

	BMI <25 n=207 (33%)		BMI 25-<30 n=215 (34%)		BMI 30-<35 n=132 (21%)		BMI ≥35 n=85 (13%)		P-value
Variable	N (%)								
Age (mean, sd)	64.6	(8.3)	67.3	(7.8)	69.1	(7.8)	65.2	(9.6)	< .001
<55	19	(9)	12	(6)	3	(2)	13	(15)	
55-69	135	(65)	122	(57)	69	(52)	40	(47)	
≥ 70	53	(26)	81	(38)	60	(45)	32	(38)	< .001
Years since diagnose (mean, sd)	4.3	(2.4)	4.2	(2.4)	4.3	(2.5)	4.5	(2.3)	.789
>2 years	43	(21)	54	(25)	26	(20)	15	(18)	
2-5 years	82	(40)	81	(38)	58	(44)	33	(39)	
>5 years	82	(40)	80	(37)	48	(36)	37	(44)	.699
FIGO stage at diagnose									
I	193	(93)	197	(92)	122	(92)	79	(93)	
II	14	(7)	18	(8)	10	(8)	6	(7)	.936
Grade									
1	100	(50)	107	(51)	56	(44)	47	(57)	
2	77	(38)	82	(39)	56	(44)	28	(34)	
3	24	(12)	22	(10)	16	(13)	7	(9)	.665
Primary treatment									
Surgery alone	160	(77)	162	(75)	97	(73)	70	(82)	
Surgery and radiotherapy	47	(23)	53	(25)	35	(27)	15	(18)	.472
Lymphadenectomy	71	(34)	68	(32)	44	(33)	26	(31)	.642
Marital status									
Partner	148	(72)	166	(78)	80	(61)	63	(74)	
No partner	59	(23)	48	(22)	52	(39)	22	(26)	.007
Education level									
Low	41	(20)	47	(22)	29	(22)	30	(35)	
Medium	135	(66)	146	(68)	91	(70)	50	(59)	
High	29	(14)	21	(10)	10	(8)	5	(6)	.042
Socio-economic status									
Low	41	(20)	44	(21)	36	(27)	19	(23)	
Middle	74	(36)	94	(44)	55	(42)	43	(52)	
High	87	(42)	69	(33)	37	(28)	18	(22)	
Elderly home	4	(2)	5	(2)	4	(3)	2	(2)	.065

Table 2 Continued.

	BMI <25 n=207 (33%)		BMI 25-<30 n=215 (34%)		BMI 30-<35 n=132 (21%)		BMI ≥35 n=85 (13%)		P-value
Variable	N (%)								
Comorbidity									
None	63	(30)	52	(24)	16	(12)	12	(14)	
One	71	(34)	58	(27)	28	(21)	17	(20)	
Two or more	73	(35)	105	(49)	88	(67)	56	(66)	<.001
Most frequent reported comorbid conditions									
Hypertension	56	(27)	93	(43)	73	(55)	54	(64)	< .001
Osteoarthritis	52	(25)	79	(37)	64	(48)	34	(40)	< .001
Backache	43	(21)	50	(23)	45	(34)	25	(29)	.037
Diabetes	14	(7)	31	(14)	34	(26)	32	(38)	<.001
Heart disease	25	(12)	30	(14)	23	(17)	9	(11)	.543
Rheumatism	21	(10)	20	(9)	11	(8)	8	(9)	.958
Depression	15	(7)	18	(8)	9	(7)	7	(8)	.946
Asthma, Chronic bronchitis, COPD	4	(2)	14	(7)	18	(14)	14	(17)	< .001

Note: Marital status included partner= married/living together; no partner =divorced/widowed/never married
Education levels included low= no/primary school; medium= lower general secondary education/vocational training; or high= pre-university education/ high vocational training/ university.
P-value report comparison between BMI-groups according to ANOVA and chi-square tests

For domains of the endometrial-specific HRQoL questionnaire (EORTC-QLQ-EN-24), univariate analyses (crude) revealed that higher BMI levels were associated with more endometrial specific problems i.e. lymphoedema symptoms, urologic problems, gastro-intestinal problems, back/pelvic pain, tingling/numbness, muscular/joint pain (Table 4). BMI was inversely associated with sexual/vaginal problems. When adjusted for socio-demographic and clinical characteristics and number of comorbidities, lymphoedema symptoms and sexual/vaginal problems remained associated with BMI. A 10 point higher BMI score led to 8.5 points more lymphoedema symptoms, 14.1 points less sexual/vaginal problems on a 0-100 scale. In univariate analyses, BMI was positively correlated with symptoms of fatigue (Table 4). The relation remained significant in multivariate linear regression analyses. A 10 point higher BMI led to a 1.0 point increase in fatigue symptoms, on a 10-50 scale.

Table 3 Mean scores on the SF-36, EORTC-EN24 and FAS for all participants and according to BMI category.

	All participants (n=666)		Normal weight BMI <25 (n=207)		Pre-obese BMI 25-<30 (n=215)		Obese class I BMI 30-<35 (n=132)		Obese class II BMI ≥35 (n=85)	
Variable	**Mean (standard deviation)**									
SF-36 (0-100)										
General health [1]	65	(21)	67	(22)	66	(20)	63	(21)	61	(20)
Physical function [1]	69	(28)	78	(24)	74	(25)	58	(28)	54	(27)
Role physical [1]	68	(41)	76	(39)	72	(39)	58	(45)	60	(42)
Bodily pain [1]	74	(25)	79	(23)	77	(22)	67	(27)	66	(26)
Vitality [1]	65	(20)	68	(20)	67	(19)	63	(19)	56	(20)
Social function[1]	82	(24)	83	(24)	84	(22)	82	(22)	76	(27)
Role emotional [1]	82	(35)	88	(29)	83	(34)	77	(40)	76	(41)
Mental health [1]	76	(17)	76	(17)	76	(18)	76	(17)	73	(19)
EORT-EN24 (0-100)										
Lymphoedema [2]	21	(26)	15	(23)	18	(23)	26	(27)	34	(30)
Urologic [2]	24	(22)	19	(21)	25	(21)	24	(21)	31	(24)
Gastro-intestinal [2]	18	(19)	16	(19)	18	(17)	19	(21)	24	(18)
Body image [2]	8.2	(18)	9.5	(19)	5.8	(15)	7.4	(17)	11	(21)
Sexual/ Vaginal problems[2]	27	(28)	35	(31)	24	(26)	19	(23)	23	(27)
Back/pelvic pain [2]	25	(29)	22	(26)	22	(27)	32	(33)	30	(33)
Tingling/ numbness [2]	19	(27)	16	(26)	17	(26)	23	(28)	24	(28)
Muscular/joint pain [2]	33	(29)	27	(26)	33	(30)	38	(28)	39	(33)
Hair loss [2]	8.6	(20)	9.4	(22)	6.6	(16)	10	(22)	8.8	(20)
Taste change [2]	4.1	(15)	4.8	(16)	3.4	(14)	4.5	(14)	3.6	(15)
Sexual Interest [1]	16	(20)	17	(21)	17	(20)	15	(21)	11	(17)
Sexual activity [1]	16	(20)	17	(22)	18	(20)	14	(19)	14	(18)
Sexual enjoyment [1]	43	(28)	43	(28)	44	(27)	48	(28)	35	(31)
FAS (10-50)										
Fatigue [2]	20	(6.8)	19	(6.4)	20	(7.0)	21	(6.3)	23	(7.6)

Note: [1]A higher score represents a higher level of satisfaction. [2] A higher score represents a higher level of symptoms or problem

Table 4 Betas of linear regression analysis evaluating the association of BMI univariate with HRQL outcomes as well as multivariate adjusting for confounding variables in model A and model B.

	All partipants (n=666)		All participants (n=666)		All participants (n=666)	
Variable	**Beta BMI univariate**		**Beta BMI Adjusted model A#**		**Beta BMI Adjusted model B #$**	
SF-36 (0-100)						
General health [1]	-0.27		-0.21		0.20	
Physical function [1]	-1.46	***	-1.30	***	-0.83	***
Role physical [1]	-1.07	***	-0.93	**	-0.30	
Bodily pain [1]	-0.80	***	-0.73	***	-0.23	
Vitality [1]	-0.70	***	-0.65	***	-0.32	*
Social function[1]	-0.45	**	-0.40	**	-0.08	
Role emotional [1]	-0.86	***	-0.76	**	-0.41	
Mental health [1]	-0.19		-0.15		0.07	
EORT-EN24 (0-100)						
Lymphoedema [2]	1.13	***	1.05	***	0.85	***
Urologic [2]	0.51	***	0.47	**	0.25	
Gastro-intestinal [2]	0.30	*	0.31	*	0.07	
Body image [2]	-0.02		0.02		-0.10	
Sexual/ Vaginal problems[2]	-1.15	***	-1.00	**	-1.41	***
Back/pelvic pain [2]	0.48	*	0.49	*	0.05	
Tingling/numbness [2]	0.52	**	0.49	**	0.26	
Muscular/joint pain [2]	0.61	**	0.58	**	-0.02	
Hair loss [2]	0.14		0.15		0.06	
Taste change [2]	-0.11		-0.13		-0.21	*
Sexual Interest [1]	-0.25		-0.19		-0.11	
Sexual activity [1]	-0.20		-0.17		-0.12	
Sexual enjoyment [1]	-0.07		-0.08		0.41	
FAS (10-50)						
Fatigue [2]	0.22	***	0.22	***	0.10	*

Note: [1]A higher score represents a higher level of satisfaction. [2] A higher score represents a higher level of symptoms or problems [#] Socio-demographic and clinical characteristics: age, years since diagnose, treatment (surgery alone, surgery and adjuvant therapy and lymphadenectomy (yes or no)), marital status, education level.[$] Comorbidities (continuous variable) ranged from 0 -10 comorbidities.
*= p< .05, **=p< .01, ***=p< .001

Figure 2 represents the amount of variance of patient reported outcomes (subscales of the SF-36, EORTC-QLQ-EN24, and FAS) explained by socio-demographic and clinical characteristics, comorbidities and BMI. For domains of the SF-36, BMI, in addition to socio-demographic and clinical characteristics and comorbid ies, significantly explained 4.3% of the variance in physical function, 0.7% in role physical (physical limitations in daily life), 1.5% in bodily pain, 1.6% in vitality and 0.9% in role emotional (emotional limitations in daily life). For scales of the EORTC-QLQ-EN, BMI explained 5.2% of the variance in lymphoedema,0.7% in urologic problems and 3.2% in sexual/vaginal problems. The additional explained variance in fatigue symptoms by BMI was 1.4%.

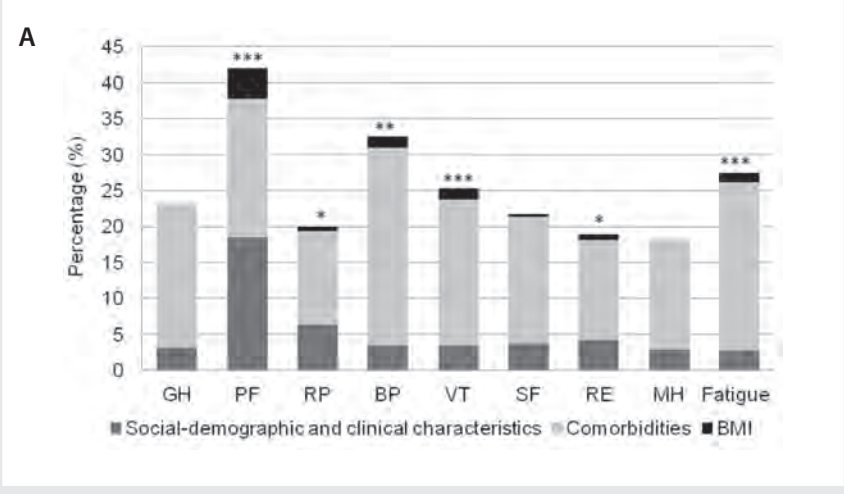

Figure 2a Explained variance (R^2 (%)) of eight domains of general HRQoL (SF-36) and fatigue (FAS) by socio-demographic and clinical characteristics (age, years since diagnose, primary treatment, marital status and education level), comorbidities (heart disease, depression, osteoarthritis, backache, other comorbidities) and BMI.

GH= general health; PF= physical function; RP= rol physical; BP=bodily pain; VT=vitality; SF=social function; RE=role emotional; MH=mental health. *= p< .05, **=p< .01, ***=p< .0001

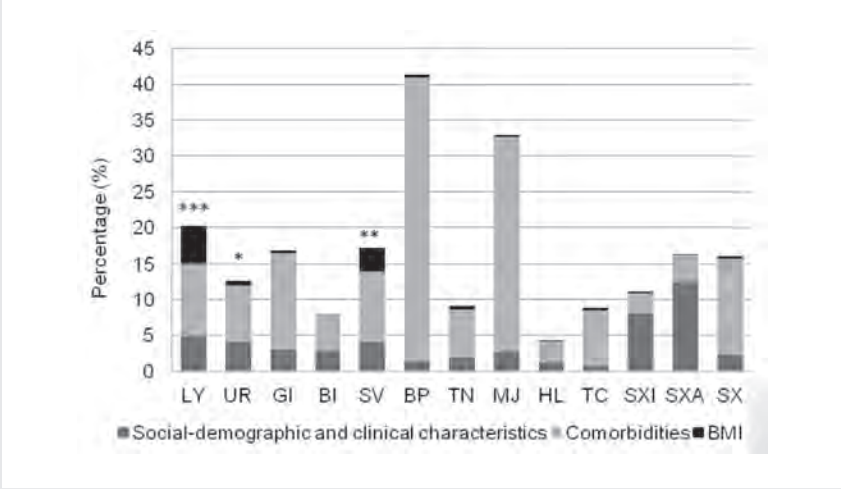

Figure 2b Explained variance (R^2 (%)) in thirteen domains of endometrial-specific QoL(EORTC-QLQ-EN24) by patient characteristics (age, years since diagnose, primary treatment, marital status and education level), comorbidities (heart disease, depression, osteoarthritis, backache, other comorbidities) and BMI.

LY= lymphoedema; UR= urologic; GI= gastro-intestinal; BI= body image; SV=sexual/ vaginal problems; BP=back/pelvic pain; TN= tingling/numbness; MJ= muscular/joint pain; HL= hairless; TC= taste change; SXI=sexual Interest; SXA= sexual activity; SXE= sexual enjoyment. *= p< .05, **=p< .01, ***=p< .001

Discussion

This population-based study showed that women with a higher BMI reported lower physical function, lower vitality, more lymphoedema symptoms, less sexual/vaginal problems and more fatigue symptoms after adjustment for socio-demographic and clinical characteristics and comorbidities. Furthermore, BMI added significantly to the explained variance of several domains of HRQoL in EC survivors i.e. physical health, role physical (problems with work or other daily activities as a result of physical health problems), bodily pain, vitality, role emotional (problems with work or other daily activities as a result of emotional problems), and lymphoedema symptoms, back/pelvic pain, fatigue symptoms and sexual/vaginal problems. However, this addition in explained variance was generally small compared to the explained variance by socio-demographic and treatment characteristics and the combination of comorbidities. Our findings support

the hypothesis that BMI has an additional impact on HRQoL outcomes in EC survivors independent of socio-demographic, clinical characteristics and comorbidities.

Our findings with regard to HRQoL domains are in line with previous studies. A study conducted among 152 women diagnosed with stage I-II EC suggests that higher BMI is associated with lower physical function and vitality [5]. A survey among 121 stage I-II EC survivors showed that patients with higher levels of BMI reported higher levels of fatigue and lower levels of physical function [7]. Another study that used different questionnaires to measure the HRQoL of EC patients, showed that BMI was associated with lower general health, higher levels of fatigue and lower functional well-being [6]. However, none of these studies specifically adjusted for potential confounding by socio-demographic and clinical characteristics and comorbidities together. Therefore, the current study is unique in showing the proportion that BMI, socio-demographic and clinical characteristics and comorbidities additionally contribute to specific HRQoL domains.

A study among 8889 randomly selected adults showed that a higher BMI was significantly associated with all SF-36 domains. This shows that BMI is associated with HRQoL within the general population as well as in an EC survivors [20].

Our findings that BMI is positively associated with lymphoedema symptoms support previous research among uterine cancer patients. An Australian study among 802 gynecological cancer survivors showed that uterine cancer survivors who were overweight had a 2.7-fold and those who were obese a 4.1-fold higher odds in developing lower limb swelling compared to their counterparts with a normal weight [21]. In our study, the differences in type of treatment (lymphadenectomy or adjuvant radiation therapy) between patients could not explain the higher reported lymphoedema symptoms among patients with a higher BMI because the analyses were adjusted for type of treatment. However, breast cancer survivors with lymphoedema symptoms report lower scores on HRQoL domains than patients without lymphoedema . This indicates that a higher BMI might be related to lower general HRQoL through lower lymphoedema. Further research should investigate the association of the triangle lymphoedema, BMI and HRQoL among EC survivors.

Remarkably, higher levels of BMI resulted in a decline of sexual/vaginal problems, such as vaginal dryness. In the general population vaginal dryness is a common symptom among postmenopausal women. Menopause is associated with a decline in estrogen level which causes vaginal atrophy [22]. Higher levels of BMI are associated with enhanced estrogen levels, due to estrogen production in fat tissue [23]. This may explain the finding that BMI positively effects the vaginal moistening and thereby overweight patients report less sexual/vaginal problems. Further research should determine the effect of BMI on vaginal dryness in endometrial cancer survivors.

Moreover, 33% of the participating women were obese (BMI ≥ 30) in the current study. This is lower than previous studies showed, where the percentage of obese EC survivors was between 50-85% [5, 7]. An explanation could be that previous studies were American studies where the prevalence of obesity in the general population is much higher compared to the prevalence of obesity in The Netherlands.

A limitation of the current study is the self-reported weight and height to calculate BMI. This can lead to an underestimation of BMI. Especially overweight or obese patients tend to underestimate their BMI score [24]. This misclassification can result in an underestimation of the association between BMI and HRQoL in EC survivors. Another limitation of the study are the self-reported comorbidities. This can lead to either an underestimation or an overestimation of the prevalence of comorbidities. This can affect the association between BMI and HRQoL in EC survivors. A third limitation is the cross-sectional study design. Although we found associations between BMI and patient reported outcomes we could not determine whether these relations were causal. A fourth limitation is the difference in time since diagnose of EC patients, which is between 0.6-9.1 years since diagnose. However, there was no association found between time since diagnosis and HRQoL domains. Finally, although there was information available on the characteristics of non-respondents and patient with unverifiable addresses, it remains unknown why non-respondents declined to participate.

Despite the limits noted, strengths could also be identified. The current study is the first which examines the mutual contribution of BMI and comorbidities on a broad spectrum of HRQoL outcomes (general, endometrial-specific and fatigue) of EC survivors. A second strength is the large population-based study sample which enhances the generalizability of this study. Another strength is the use of well-established and endometrial specific measures of HRQoL. Finally, confounders were literature based and identified a priori, which makes the corrected results (even more) reliable.

In conclusion, for the large group EC survivors their HRQoL after cancer and treatment is critical. Since many survivors are overweight or obese, we want to understand the effect of BMI on HRQoL. This study showed that BMI is related to several HRQoL outcomes and that BMI has an important contribution to HRQoL domains next to the contribution of comorbid conditions, socio-demographic, and clinical characteristics. These findings are relevant for clinical practice, for educating patients, and for the interpretation and treatment of complaints. Also, BMI needs to be taken into account in HRQoL studies for instance by adjusting for BMI besides comorbidities. Moreover, weight loss in overweight/obese menopausal women possibly improves HRQoL and might be an important goal for EC survivors. Future research should assess if interventions to decrease BMI in obese EC survivors improve HRQoL.

References

[1] Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61: 212-36.

[2] Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. Curr Oncol Rep 2010;13: 71-6.

[3] Boll D, Verhoeven RH, van der Aa MA, Pauwels P, Karim-Kos HE, Coebergh JW, van Doorn HC. Incidence and survival trends of uncommon corpus uteri malignancies in The Netherlands, 1989-2008. Int J Gynecol Cancer 2008;22: 599-606.

[4] Sirtori A, Brunani A, Villa V, Berselli ME, Croci M, Leonardi M, Raggi A. Obesity Is a Marker of Reduction in QoL and Disability. ScientificWorldJournal 2012: 167520.

[5] Fader AN, Frasure HE, Gil KM, Berger NA, von Gruenigen VE. Quality of life in endometrial cancer survivors: what does obesity have to do with it? Obstet Gynecol Int 2011: 308609.

[6] Courneya KS, Karvinen KH, Campbell KL, Pearcey RG, Dundas G, Capstick V, Tonkin KS. Associations among exercise, body weight, and quality of life in a population-based sample of endometrial cancer survivors. Gynecol Oncol 2005;97: 422-30.

[7] Basen-Engquist K, Scruggs S, Jhingran A, Bodurka DC, Lu K, Ramondetta L, Hughes D, Carmack Taylor C. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. Am J Obstet Gynecol 2009;200: 288 e1-8.

[8] von Gruenigen VE, Gil KM, Frasure HE, Jenison EL, Hopkins MP. The impact of obesity and age on quality of life in gynecologic surgery. Am J Obstet Gynecol 2005;193: 1369-75.

[9] Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern The Netherlands 1995-2008. Eur J Cancer 2011;47: 1504-10.

[10] Smith AW, Reeve BB, Bellizzi KM, Harlan LC, Klabunde CN, Amsellem M, Bierman AS, Hays RD. Cancer, comorbidities, and health-related quality of life of older adults. Health Care Financ Rev 2008;29: 41-56.

[11] van de Poll-Franse LV, Horevoorts N, van Eenbergen M, Denollet J, Roukema JA, Aaronson NK, Vingerhoets A, Coebergh JW, de Vries J, Essink-Bot ML, Mols F. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011;47: 2188-94.

[12] Nicolaije KA, Husson O, Ezendam NP, Vos MC, Kruitwagen RF, Lybeert ML, van de Poll-Franse LV. Endometrial cancer survivors are unsatisfied with received information about diagnosis, treatment and follow-up: a study from the population-based PROFILES registry. Patient Educ Couns 2012;88: 427-35.

[13] van de Poll-Franse LV, Pijnenborg JM, Boll D, Vos MC, van den Berg H, Lybeert ML, de Winter K, Kruitwagen RF. Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study. Gynecol Oncol 2012;127: 153-60.

[14] James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res 2001;9: 228S-233S.

[15] Van Duijn C, Keij I. Sociaal-economische status indicator op postcodeniveau [in Dutch]. Maandstatistiek van de bevolking 2002;50: 32-35.

[16] Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum 2003;49: 156-63.

[17] Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51: 1055-68.

[18] Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, Galalae R, Schmalz C, Barlow E, Jensen PT, Waldenstrom AC, Bergmark K, Chie WC, Kuljanic K, Costantini A, Singer S, Koensgen D, Menon U, Daghofer F. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 2011;47: 183-90.

[19] de Kleijn WP, De Vries J, Wijnen PA, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. Respir Med 2011;105: 1388-95.

[20] Doll HA, Petersen SE, Stewart-Brown SL. Obesity and physical and emotional well-being: associations between body mass index, chronic illness, and the physical and mental components of the SF-36 questionnaire. Obes Res 2000;8: 160-70.
[21] Beesley V, Janda M, Eakin E, Obermair A, Battistutta D. Lymphedema after gynecological cancer treatment: prevalence, correlates, and supportive care needs. Cancer 2007;109: 2607-14.
[22] Simon JA. Identifying and treating sexual dysfunction in postmenopausal women: the role of estrogen. J Womens Health (Larchmt) 2002;20: 1453-65.
[23] Repse-Fokter A, Takac I, Fokter SK. Postmenopausal vaginal atrophy correlates with decreased estradiol and body mass index and does not depend on the time since menopause. Gynecol Endocrinol 2008;24: 399-404.
[24] Gillum RF, Sempos CT. Ethnic variation in validity of classification of overweight and obesity using self-reported weight and height in American women and men: the Third National Health and Nutrition Examination Survey. Nutr J 2005;4: 27.

5

Discussion

5.1. Point of view : Debate on the applicability of survival improvement and reduction of mortality in the elderly with unfavourable types of uterine malignancies

5.2. General discussion

5.1

Point of view : Debate on the applicability of survival improvement and reduction of mortality in the elderly with unfavourable types of uterine malignancies

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Point of view : Debate on the applicability of survival improvement and reduction of mortality in the elderly with unfavourable types of uterine malignancies

Endometrial carcinoma (EC) is the most common gynaecological malignancy and in the western world, and it is the fourth most common type of cancer in women after breast cancer, lung cancer, and cancer of the intestines[1]. Over the last decades its incidence has increased and a further increase is expected. This paper focuses on endometrioid endometrial carcinomas (EEC) and the non-endometrioid endometrial carcinomas (NEEC), which encompass respectively 80% and 15% of uterine malignancies[2]. Recently we published data on the incidence and survival of ECC in a cohort of Dutch women; the median age for EEC was 66 years and for NEEC it was 70 years[2]. Early stage EEC (FIGO I and II) was present in 77% of the cases, in which TH-BSO was performed in 98% women[3]. The relative five-year survival rate for EEC was 90%[4]. If we focus on the group of women with poorly differentiated (grade 3) type EEC, higher stage EEC (FIGO III and IV), or an unfavourable histological type like NEEC results are poor: the five-year survival rate for a grade 3 EEC is 58%, for FIGO III and IV EEC it is 55% and 21%, respectively, and for NEEC it is 54%, including serous adenocarcinoma 51% and carcinosarcoma 37%[2, 4, 5]. Only modest progress was noted in the five-year survival rate[2, 4], and it appears that in recent decades mortality remained stable. [6]

This article is a contribution to the discussion on how the survival of elderly women with grade 3 EEC, advanced stage EEC, and NEEC can be improved and how mortality due to malignancies of the uterine body can be reduced. So far, solutions are mainly sought in changing the treatment strategy. The number of publications on this topic increases every year[5, 7-10]. This is promising, however most strategies are still under investigation. The gynaecologic cancer intergroup(GCIG) trail[11] on lymphadenectomy might improve insight in the benefit of lymph node sampling/dissection.[12-15] PORTEC-3[16] is an ongoing phase III trial in which pelvic radiation combined with concurrent and adjuvant chemotherapy is compared with pelvic radiation alone in high risk EEC. In case of advanced stages, cytoreductive surgery seems to improve the chances of survival, but randomised studies failed to demonstrate this effect [9, 17]. It is still debatable whether adjuvant chemotherapy, often a combination of carboplatine and paclitaxel (Taxol) is beneficial in EEC. Several publications demonstrate a positive effect on survival [5, 8], particularly in advanced stage EEC and NEEC. However, the number of women treated in these studies are small and the study population is heterogeneous. In a recent population based study on adjuvant treatment in EEC in the period between 1994 and 2009[18], chemotherapy was more given in advanced stage disease, without an advantage in terms of improved survival[18].

In the foregoing we discussed the tumour characteristics, occurring more often in the elderly, that lead to poor survival and addressed the subject of developing treatment strategies. Survival and mortality, however, are largely determined by patient health condition and other characteristics.

Age is an independent risk indicator for a poor prognosis in case of EC [19-23]. In recent literature 75 years is taken as the cut-off point for the definition of the elderly [4, 24, 25]. In case of EEC the relative five-year survival rate of women < 75 years old compared to women of 75+ years is 90% and 76%, respectively[4]; and for NEEC it is 60% and 40%, respectively[2, 4]. Most deaths due to uterine malignancies occur in the group of elderly women. This poorer survival rate is explained by the increased risk of mortality as a result of additional illness, poor tumour characteristics, less extensive surgery and/or chemotherapy and therapy-related deaths in the elderly[26]. Between the age of 70 and 75 years we see a shift from mono-morbidity to multi-morbidity in large groups of patients with a newly diagnosed malignancy[26]. These multi-morbidities consist of diabetes mellitus (DM), cardiovascular diseases, chronic obstructive pulmonary disease, hypertension, and a previous malignancy. The survival decreases considerably in patients with co-morbidity. With regards to the treatment of women with EEC, it appears from the literature that 'fit' elderly patients can tolerate surgery well at advanced ages, especially if minimally invasive techniques, such as laparoscopic and robot surgery, are used[27-29]. In high stage disease laparotomic surgery is performed in merely 55% of cases, compared to 70% in younger women[18]. Little is known about chemotherapy in the elderly since most clinical trials encompass only a small, selected pool of elderly patients. Studies on ovarian cancer in which carboplatine and paclitaxel (Taxol), showed that this regiment is tolerated well by 'fit' elderly patients, yet often it is decided against treatment on the basis of age[30]. For RT a similar effect is seen; it appears that elderly patients receive (indicated) adjuvant RT less often, whilst they seem to tolerate it well[3].

Currently, elderly women are excluded from clinical trials on the basis of their co-morbidities. Consequently, new insights from (ongoing) studies will not apply to this patient group.[24, 30]. A new definition of, and suitable selection of 'fit' elderly patients, who are able to participate in clinical trials, is needed. At the same time, it is important to identify 'non-fit' elderly, who will not be offered extended treatment, that will not be beneficial for them. In geriatric literature several definitions of 'non-fit' or vulnerable elderly are in use[31-33]. Physical and functional limitations, and psychological and social parameters are involved. Quality-of-life studies showed that after treatment elderly patients have higher scores on fatigue and depression for a longer period in comparison to younger patients[30, 34, 35]. The time-to-benefit depends on the tumour, but certainly also on co-morbidity, self-reliance and nutritional state of the elderly patient. The preferences of elderly are different to those of younger patients and there is much inter-individual variation within this age group[30]. The mortality risk should be only one of the outcomes on which the choice of treatment is based, other factors are equally relevant, but they are described less often in the literature.

Conclusion

The answer to the question whether, in case of unfavourable endometrial carcinoma, survival can be improved and mortality reduced seems to depend first and foremost on the health condition of the patient. We state that the outcome of EEC in higher age group should be monitored not only by survival, but merely by QoL and patient satisfaction. Unfavourable tumour characteristics, grade 3 EEC, advanced stage EEC, and NEEC occur often in elderly women (≥75 years), amongst whom vulnerability and multi-morbidity are highly prevalent, which in turn results in low five-year survival rates and increased mortality. Aspirations to improve survival should be put into perspective for this group of patients because, due to factors such as the burden of treatment and convalescence, priority for them lies not with longevity, the impact on self-reliance, and their perspective on life, but rather with symptom management. Elderly patients, who are fit and vital according to a geriatric assessment, appear to cope well with extensive surgery, preferably with minimally invasive techniques, as well as adjuvant treatment with radiotherapy and chemotherapy. It is advisable that these fit and vital elderly patients be involved in clinical trials more than was the case up to now, so as to arrive at an evidence-based choice for a meaningful treatment strategy.

Reference List

[1] Jemal A., Bray F., Center M.M., Ferlay J., Ward E., Forman D. Global cancer statistics. *CA Cancer J Clin* ;**61**:69-90;2011

[2] Boll D., Verhoeven R.H., Aa van der M.A., Coebergh J.W., Doorn van H.C. Incidence and survival trends of uncommon corpus uteri malignancies in the Netherlands, 1989-2008. *Int J Gynecol Cancer* ;**22**:599-606;2012

[3] Boll D., Verhoeven R.H., van der Aa M.A., Lybeert M.L., Coebergh J.W., Janssen-Heijnen M.L. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. *Eur J Cancer* ;**47**:1504-10;2011

[4] Boll D., Karim-Kos H.E., Verhoeven R.H., Poll-Franse L., Burger C.W., Coebergh J.W. et al. Increased incidence and improved survival in endometrioid endometrial cancer diagnosed since 1989 in The Netherlands: A population based study. *Eur J Obstet Gynecol (2012)* ;2012

[5] Wright J.D., Barrena Medel N.I., Sehouli J., Fujiwara K., Herzog T.J. Contemporary management of endometrial cancer. *Lancet* ;**379**:1352-60;2012

[6] Statistics Netherlands. http://statline.cbs.nl/StatWeb. *Accessed January* ;2011

[7] Amant F., Moerman P., Neven P., Timmerman D., Van L.E., Vergote I. Endometrial cancer. *Lancet* ;**366**:491-505;2005

[8] Vandenput I., Trovik J., Vergote I., Moerman P., Leunen K., Berteloot P. et al. The role of adjuvant chemotherapy in surgical stages I-II serous and clear cell carcinomas and carcinosarcoma of the endometrium: a collaborative study. *Int J Gynecol Cancer* ;**21**:332-6;2011

[9] van Wijk F.H., van der Burg M.E., Burger C.W., Vergote I., van Doorn H.C. Management of surgical stage III and IV endometrioid endometrial carcinoma: an overview. *Int J Gynecol Cancer* ;**19**:431-46;2009

[10] De Jong R.A. Molecular and biological nature of endometrial cancer. *Thesis nov* ;2012

[11] Concept lymphadectomy trial. Gynecolgic Cancer Intergroup. *www gcig igcs org* ;2013

[12] Mariani A., El-Nashar S.A., Dowdy S.C. Lymphadenectomy in endometrial cancer: which is the right question? *Int J Gynecol Cancer* ;**20**:S52-S54;2010

[13] Kitchener H., Swart A.M., Qian Q., Amos C., Parmar M.K. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet* ;**373**:125-36;2009

[14] van de Poll-Franse LV, Pijnenborg J.M., Boll D., Vos M.C., van den Berg H., Lybeert M.L. et al. Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: A large population-based study. *Gynecol Oncol* ;2012

[15] Tong S.Y., Lee J.M., Lee J.K., Kim J.W., Cho C.H., Kim S.M. et al. Efficacy of para-aortic lymphadenectomy in early-stage endometrioid uterine corpus cancer. *Ann Surg Oncol* ;**18**:1425-30;2011

[16] studies. Dutch Gynecolig Oncology Group. *www DGOG nl* ;2013

[17] van Wijk F.H., Huikeshoven F.J., Abdulkadir L., Ewing P.C., Burger C.W. Stage III and IV endometrial cancer: a 20-year review of patients. *Int J Gynecol Cancer* ;**16**:1648-55;2006

[18] Boll D., Pijnenborg J.M., Nout R.A., Lybeert M.L., Poll-Franse L., Coebergh J.W. et al. Reduced adjuvant radiotherapy based on increasingly evidence-based treatments of patients with endometrioid endometrial carcinoma resulting in similar survival in the Netherlands between 1994-2009. *Eur J Cancer* ;2013

[19] Vance S., Yechieli R., Cogan C., Hanna R., Munkarah A., Elshaikh M.A. The prognostic significance of age in surgically staged patients with Type II endometrial carcinoma. *Gynecol Oncol* ;**126**:16-9;2012

[20] Bucy G.S., Mendenhall W.M., Morgan L.S., Chafe W.E., Wilkinson E.J., Marcus R.B., Jr. et al. Clinical stage I and II endometrial carcinoma treated with surgery and/or radiation therapy: analysis of prognostic and treatment-related factors. *Gynecol Oncol* ;**33**:290-5;1989

[21] Ahmed A., Zamba G., DeGeest K., Lynch C.F. The impact of surgery on survival of elderly women with endometrial cancer in the SEER program from 1992-2002. *Gynecol Oncol* ;**111**:35-40;2008

[22] Wright J.D., Lewin S.N., Barrena Medel N.I., Sun X., Burke W.M., Deutsch I. et al. Endometrial cancer in the oldest old: Tumor characteristics, patterns of care, and outcome. *Gynecol Oncol* ;**122**:69-74;2011

[23] Fleming N.D., Lentz S.E., Cass I., Li A.J., Karlan B.Y., Walsh C.S. Is older age a poor prognostic factor in stage I and II endometrioid endometrial adenocarcinoma? *Gynecol Oncol* ;**120**:189-92;2011

[24] Hoon S.D., Kang S., Lim M.C., Lee T.S., Park J.Y., Kim T.J. et al. Management of the elderly patient with gynecologic cancer: report of the 2011 workshop in geriatric gynecologic oncology. *Int J Gynecol Cancer* ;**22**:161-9;2012

[25] Ueda S.M., Kapp D.S., Cheung M.K., Shin J.Y., Osann K., Husain A. et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. *Am J Obstet Gynecol* ;**198**:218-6;2008

[26] Janssen-Heijnen M.L., Houterman S., Lemmens V.E., Louwman M.W., Maas H.A., Coebergh J.W. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol* ;**55**:231-40;2005

[27] Frey M.K., Ihnow S.B., Worley M.J., Jr., Heyman K.P., Kessler R., Slomovitz B.M. et al. Minimally invasive staging of endometrial cancer is feasible and safe in elderly women. *J Minim Invasive Gynecol* ;**18**:200-4;2011

[28] Wright J.D., Burke W.M., Wilde E.T., Lewin S.N., Charles A.S., Kim J.H. et al. Comparative Effectiveness of Robotic Versus Laparoscopic Hysterectomy for Endometrial Cancer. *J Clin Oncol* ;2012

[29] Mourits M.J., Bijen C.B., Arts H.J., ter Brugge H.G., van der Sijde R., Paulsen L. et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. *Lancet Oncol* ;**11**:763-71;2010

[30] Maas HA. Unravelling Hterogeneity in Elderly patients. *Thesis isbn-978-90-9026372-4* ;2012

[31] Ferrucci L., Guralnik J.M., Cavazzini C., Bandinelli S., Lauretani F., Bartali B. et al. The frailty syndrome: a critical issue in geriatric oncology. *Crit Rev Oncol Hematol* ;**46**:127-37;2003

[32] Hamaker M.E., Jonker J.M., de Rooij S.E., Vos A.G., Smorenburg C.H., van Munster B.C. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol* ;**13**:e437-e444;2012

[33] Pal S.K., Katheria V., Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. *CA Cancer J Clin* ;**60**:120-32;2010

[34] Oldenburg CS, Boll D., Nicolaije K.A., Vos M.C., Pijnenborg J.M., Coebergh J.W. et al. The association of BMI and other comorbidities on quality of life and fatigue of endometrial cancer survivors: a study from the population-based PROFILES registry. *Eur J Cancer Prev* ;2012

[35] van de Poll-Franse LV, Mols F., Gundy C.M., Creutzberg C.L., Nout R.A., Verdonck-de Leeuw I.M. et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer* ;**47**:667-75;2011

5.2

General discussion

In chapter 1 the aim of the study and an overview of the literature was presented. Chapter 2 described the trends in corpus uteri malignancies in population-based studies using data from the Dutch National Cancer Registry (NCR) from 1989 to 2009 and a description of the effects on survival of the implementation of evidence-based treatment like the results of PORTEC-1[1] and PORTEC-2[2]. In chapter 3 patient characteristics were analysed, such as age and co-morbidity, on treatment and survival in women with early stage endometrioid endometrial cancer (EEC), based on data from the Eindhoven Cancer Registry from 1995 to 2008. In addition, chapter 3 evaluated the adherence to national guidelines and investigated the role of co-morbidity. In Section 3.2 a retrospective cohort study was presented on the influence of DM on cancer stage at diagnosis, cancer recurrence, and survival of endometrial cancer (EC) patients. In Chapter 4 the influence of co-morbidity was presented, such as higher BMI, on the quality of live in EC survivors. This analysis was conducted using data from the PROFILES Registry from 1999 to 2007. In section 5.1. the question whether we might be able to improve survival and decrease mortality in the elderly with unfavourable corpus uteri malignancies was discussed.
In this section, a general discussion of the main findings of this thesis on the epidemic of corpus uteri malignancies is presented in two parts: an oncological viewpoint with implications for clinical practice, and the approach to life expectancy for patients with EEC. The oncologic point of view includes a clinical reality based on newly diagnosed cases according to stage and histological type, survival and mortality, followed by potential implications of these trend findings for clinical practice. The second part of the thesis reveals that life expectancy for the majority of patients with EEC is related to patient characteristics including age, concomitant diseases, such as diabetes mellitus, and a high body mass index (BMI). Quality of care and quality of life considerations are also discussed. Finally, recommendations are provided for prevention strategies and for future research.

Trends in corpus uteri malignancies between 1989-2009

A total of 32,332 women with a newly diagnosed corpus uteri malignancy were registered in the NCR between 1989 and 2009. The majority (80%) of the corpus uteri malignancies were the EEC. The less common types of corpus uteri malignancies were serous adenocarcinoma, clearcell carcinoma, carcinosarcoma, which are also classified as non-endometrioid endometrial carcinomas (NEEC), constituted 12% of the corpus uteri malignancies. A minority (4%) comprised the mesenchymal corpus uteri malignancies, also referred to as sarcomas.

Trends in EEC

Increase incidence of EEC stage I and grade 1&2 with good prognosis

Chapter 2.1 presented the significant increase in incidence (ESR) of corpus uteri malignancies over the past two decades. This rising incidence is mainly due to the growing number of women diagnosed with EEC. The most pronounced increase in EEC is seen in

stage Ib (FIGO 1988: < 50% invasion of the myometrium) and grade 1&2, also called the low risk EEC. The strongest association with enhanced EEC risk is obesity, defined as the BMI > 30 kg/m^2. Excess weight leads to increased adipose tissue. In adipose tissue, androgens are converted to estrogen, leading to increased endogenous estrogen exposure[3,4]. In the Netherlands, the percentage of obese (BMI> 30 kg/m^2) adult women increased from 6% in 1990 to 13% in 2010[5]. If obesity could be prevented, it is estimated that the avoidable cases of endometrial cancer would be reduced by 45-53% in Europeans[6,7]. It is predicted that an increasing number of obese women will need a total hysterectomy, preferably with minimal invasive surgery[8-10].
For EEC, the increase in the 5-year relative survival was 90% for FIGO stage I in 1989-94 to 94% in 2005-09 ($p<0.001$) and 89% to 93% ($p<0.001$) for grade 1&2. Gynaecologists need to be prepared for an increasing number of women with higher BMI's, who need minimal invasive surgery such as laparoscopic or robotic surgery. Several studies have been published on this topic[11-14]. In 2009, 8.7 per 10,000 women in the Netherlands were treated with a hysterectomy and 0.7 per 10,000 women were treated with a total laparoscopic hysterectomy (TLH) or a laparoscopic assisted vaginal hysterectomy (LAVH) (figure 1)[15]. Data for 2013 are not yet available, but the expectation is that the percentage of laparoscopic hysterectomies for EEC has continued to increase. Hence, gynaecologists and trainees need to be educated in laparoscopic surgery. it becomes increasingly more important to use minimal invasive surgery, especially in obese patients, to achieve quicker mobilisation, fewer wound infections and dehiscence, and shorter hospital stays.

Survival gap between age < 60 compared to age group 75 years and older

In the period 2005-2009, the overall 5-year relative survival for women with EEC < 60 years was 92% and for women of 75 years and older it was 76%. One of the explanations for these survival rates is the difference of stage distribution between the age groups. We observed that 10% of the patients of 45-59 years had advanced stages compared to 20-22% of patients 75 years and older. Another explanation is the greater proportion of women with grade 3 histology in the age group of 75 years and older. In chapter 3 we presented other important influences on survival in the older age group, such as co-morbidity, diabetes and adherence to treatment guidelines for adjuvant therapy.
The 5-year relative survival during the period of 1989-1994 for grade 3 was 60% and remained almost the same (61%) in period 2005-2009. Stage III showed a survival of 54% in first period and 55% in the later period, while stage IV showed an increase from 13% to 21%, but number of patients with stage IV were too low to calculate statistical significance. These results indicate a lack of improvement in survival for patients with advanced stages and/or with high grade EEC. Also overall a lack of improvement is seen in the older patients. Results of ongoing and newly planned clinical trials (such as PORTEC-3 and Gynaecologic Cancer Intergroup GCIG lymphadenectomy trial) may provide opportunities to study new treatment strategies and possibilities to improve the survival for women

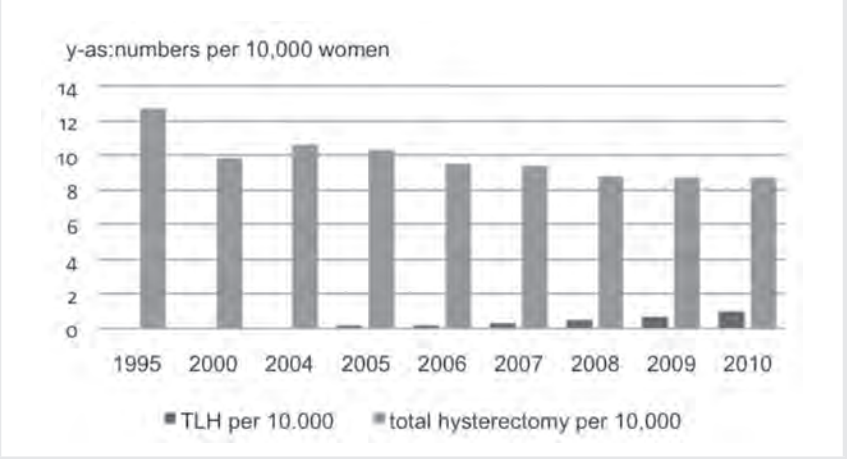

Figure 1 Number of total laparoscopic hysterectomy (TLH) per 10,000 women. (Cbs statistics).

with high risk EEC. Ongoing trials, however, do not include the high percentage of women with advanced stages and older women with grade 3 EEC and those suffering from concomitant diseases. Improvement in health status in elderly patients is dependent on many other factors (i.e. multi morbidity, dependence on functional status and frailty) besides improvement in survival. We must acknowledge that, at the population level, improvement in survival is limited by factors beyond the influence of treatment strategies.

Progression against EEC: Is progress optimal?

We used the framework proposed by H. Karim-Kos[16] to assess progress against EEC by combining the parameters incidence, survival and mortality. Progress is considered optimal when incidence decreases and/or survival improves and mortality decreases. The incidence of EEC significantly increased during the past three decades and is expected to increase further in the coming decade. In the Netherlands, an increase in absolute incidence of EEC is expected from 1783 patients in 2007 to 2500 in 2020[17]. The overall 5-year relative survival increased from 83% to 85% for EEC between 1989 and 2009. Mortality rates decreased from 1989 to 2009, but with the joint point analysis rates have remained stable since 1992 (chapter 2.1). Limitations of mortality rates are that they are based on cause of death statistics, which are not very reliable. Unfortunately, mortality data are for the total of corpus uteri malignancies (C54) and are not specified for EEC, NEEC or sarcomas. Furthermore, trends in competing risks of death, especially among the older patients, may complicate the interpretation of the cancer mortality trend. The

mortality rates reflect the risk of cancer death among patients diagnosed over the preceding years. During the past decades, more women have been diagnosed with uterine cancer, yet mortality remained stable. This can be considered an improvement. We conclude that optimal progress has been made in the treatment of EEC because survival rates have increased and mortality rates have stabilised, despite the increase of EEC incidence.

Mortality

While optimal progress has been made against EEC, mortality is still approximately 18% of all women diagnosed with a corpus uteri malignancy. In other words, of 1800 new cases per year 300-350 women per year still die of corpus uteri malignancy. The 5-year relative survival rates for EEC are greatest at 92% in the group of 60 years and younger and remained stable between 1989-2008. In the group of 75 years and older improvement in survival was 72-76%. It is expected that this improvement in survival can lead to a decrease in mortality in the coming years. Unfortunately, the survival rates for NEEC are much lower and these data are presented in chapter 2.3. The expected mortality for this group remains high and is mainly responsible for ultimate mortality. The literature shows that clear-cell carcinoma and serous carcinoma made up only about 10-12% of the corpus uteri malignancies, but they are associated with about 50% of relapses[18;19]. Therefore, although progress has been made, there is still a need for improvement in outcome for women with a high risk of EEC, with advanced stages, and with NEEC or sarcomas.

Trends in NEEC

In Chapter 2.3, the epidemics of NEEC and sarcomas in the Netherlands for the period 1989 and 2008 showed a significant decline in incidence of serous carcinoma, also called Uterine Papillary serous carcinoma, after 1994[20]. This was due to a more accurate differentiation between villoglandular EAC and serous carcinomas, as well as to improvements in histopathological diagnosis. Survival of serous carcinoma during the period after 1994 corresponded better with the outcome of serous carcinoma in several other population-based studies from the SEER database USA and Norwegian cancer registry[19;21;22]. For analysis with data of NCR concerning NEEC, classification changes have made the data before 1999 less reliable. For sarcomas we recommend that data before 2004 should not be used. Similarly, population-based studies of NEEC with unrevised pathology are of less value because of the aforementioned changes in classification. In general, we conclude that the incidence of NEEC did not increase between 1989 and 2008. The median age remained at 68. For the clearcell, the median age remained at 71, while for the very rare tumours such as neuroendocrine and mixed tumours, the median age was 75 years. 5-year relative survival during 2004-2008 was 60% and declined to 40% for women of 75 years and older.

Trends in sarcomas

Sarcomas accounted for 4.2% of all corpus uteri malignancies. The most frequently diagnosed sarcoma was leiomyosarcoma (LMS) followed by endometrial stromal cell sarcoma (ESS). Progress in histopathological diagnosis was observed by the change in incidence and survival of ESS. After the publication by Amant[23] about histopathological classification of ESS in 2004, the differentiation between low and high grade ESS became more accurate. This is reflected by the increased incidence of low grade ESS, with a 5-year relative survival of 95% during 2004-2008, as well as a decrease in incidence and survival for patients with high grade ESS. Accurate histopathological diagnosis of rare corpus uteri tumors is of increasing complexity and we recommend that (inter)national expert groups of pathologists and clinicians are formed. It is of vital importance for clinical decisions to obtain the best possible diagnosis for prognostic and therapeutic implications. Centralisation of patient information for rare tumours (incidence < 6 per 100,000) at the national and/or international level is necessary to improve knowledge about diagnostic and therapeutic procedures and prognostic factors.

Trends in carcinosarcoma, previously known as malignant müllerian mixed tumor

We conducted a separate analysis on the carcinosarcomas, previously known as malignant müllerian mixed tumour, because our analysis started in 1989 and at that time it was thought that malignant mixed müllerian tumor represented a sarcoma. We found an uncertain relationship between epithelial and mesenchymal malignant cells; however, since 1997[24], these malignancies have been considered to be metaplastic carcinomas, the behaviour of which is determined by the epithelial element. Currently carcinosarcomas are classified under the NEEC tumor type[25,26]. We expected a rise of carcinosarcomas, because several studies described a relationship between tamoxifen use (adjuvant therapy in hormone sensitive breast cancer) and carcinosarcomas[27-30]. In the large population-based study described in chapter 2.3, we could not confirm the predicted increase of carcinosarcomas. Median age of patients with carcinosarcoma was 71 years, 5 years greater than the median age of 66 years for EEC. The 5-year relative survival for patients with carcinosarcomas was only 35%, and for women of 75 years and older only 25%. In summary, the relationship between tamoxifen use and a greater incidence of less favorable histology of endometrial carcinoma is less clear in practice than formerly expected. Carcinosarcoma occurred more frequently in older women and had a poor prognosis, especially for women of 75 years and older. In general, we conclude that in the Netherlands tumor diagnosis and classification improved between 1989 and 2008. The survival rates of NEEC and sarcomas were much lower than for EEC, especially in elderly patients.

Trends in treatment of EEC patients between 1994-2009

Between 1994 and 2009, 20,386 women were diagnosed with EEC, and the majority of these women had stage IB en IC. A significant decrease occurred in adjuvant radiotherapy for stage I in the group 45-59 years of age. A significant increase in adjuvant radiotherapy occurred in stage IC for groups of 60 years and older in the period 1994-2009. Furthermore, since 2007 an increasing trend is seen in adjuvant radiotherapy in stage I EEC for group of 80+ years of age. The 5-year relative survival did not change over time for stages I and II. The prognostic factors such as age and grade have a significant influence on the RER and on survival. A significant decrease of adjuvant radiotherapy occurred in stage I EEC between 1994 and 2009 without an influence on survival. The successful implementation of the results of RCT PORTEC-1[1] led to reduction of overtreatment. Introduction of the results of PORTEC-2[2] led to reduction of undertreatment in the elderly patients in low to intermediate EEC.

Role of co-morbidity

Prevalence of co-morbidity in patients with EEC increased over the past 16 years and is expected to increase further due to an aging population with an unhealthy lifestyle. Specifically, the patients over 75 years have a high prevalence of co-morbidity. EEC is a cancer with a good prognosis and in these cancer types relative survival statistics have a limited clinical relevance, because relative survival and observed survival differ. The observed survival reflects the effects of both non-cancer and cancer-related causes of death. Therefore, the influence of patient characteristics was explored including age and co-morbidity, such as cardiovascular disease, previous malignancy and diabetes mellitus, on treatment and survival. Co-morbidity was defined as a life-shortening disease that was present at the time of cancer diagnosis[31]. Co-morbidity is registered in the Eindhoven cancer registration (ECR) and this was unique, because other registries do not contain these data.

Adherence to national guidelines and influence of co-morbidity on survival

In chapter 3.1 the analysis of 2099 patients diagnosed between 1995 and 2008 with stage I EEC showed that the majority of the patients (98-99%) underwent total hysterectomy with bilateral oophorectomy (TH-BSO). Using the population-based data analysis, we confirmed that the results of Portec I were well implemented in the Netherlands. In low to intermediate risk EEC, which account for more than half of EEC patients, the five year survival rate is high, 90%. Survival was clearly poorer for patients with stage I EEC with co-morbidity compared to patients without co-morbidity. Survival in patients with co-morbidity declined to 74%, especially for those with diabetes, cardiovascular disease and previous malignancy. For EEC, adherence to guidelines was analysed and showed that in 98% of cases a hysterectomy was performed. The cause of death was unknown and we could not evaluate whether patients with co-morbidity had a greater risk of dying

Table 1 Crude univariate 5-year survival and multivariable Hazard ratios (HR) for endometrial cancer FIGO stage I in the south of the Netherlands 1995-2008 (n=1770).

		n	(%)	5-year survival (%)	HR [3]	[4]95%CI
Number of co-morbidity	0	721	41%	91%	Ref	
	1	605	34%	88%	1.4	1.0-1.9*
	2+	444	25%	74%	3.0	2.2-3.9
Type co-morbidity[2]	Cardiovascular	281	16%	76%	2.3	1.7-3.2
	Diabetes	304	17%	74%	2.9	2.2-4.0
	Hypertension	596	34%	82%	1.8	1.4-2.4
	Previous cancer	232	13%	75%	2.6	1.9-3.7

as a result of endometrial cancer or of the co-morbidity. Although less administration of adjuvant radiotherapy was observed in relation with age and co-morbidity[32;33], this had no influence on survival.

Role of diabetes mellitus in women with EEC and the effect of EEC on diabetes regulation

The lower survival rates observed in patients with diabetes mellitus (DM), described in chapter 3.1, should be investigated further. DM is known as a prognostic factor for EEC in postmenopausal patients, but cause of death has never been properly investigated for patients with EEC, making it difficult to understand whether the observed increased overall mortality can simply be explained by an effect of DM or is a true effect of interaction between the two diseases. Therefore we conducted a retrospective cohort study (see chapter 3.2). A sub cohort of 193 DM patients were matched with a sample of 195 EEC patients without DM. The disease specific mortality in patients with EEC and DM was equal to patients without DM. The conclusion is that the increased risk of death in EEC is associated with the comorbid condition itself. The hypothesis that EC has a negative effect on the course of DM was rejected, because DM treatment and DM complications did not change significantly when patients were compared before and after EC diagnosis and treatment. An intriguing finding of this study was a deeper myometrial invasion at time of diagnosis in DM patients. Probably the symptom of abnormal vaginal blood loss is overshadowed by symptoms of comorbidities or is ignored in DM patients and their care

providers**.** A limitation of the study is that the analysis for EC-specific mortality was underpowered due to the relatively small number of patients in the sub cohort.
In chapter 3.3, the increase of co-morbidity over the past 16 years was related to three factors in the general population and the EEC population: i. an ageing population, ii. improved care for chronic diseases in the elderly, with an improved survival, and iii. lifestyle changes. An increase was seen in consumption of meat, dairy products and alcoholic beverages, together with the reduction in physical activity and a large increase in prevalence of obesity[7;34]. It is not surprising that diabetes mellitus occurred in a high proportion of patients with EEC, because diabetes associated with a two-fold increased risk for endometrial cancer[35]. The number of newly diagnosed cancer patients with DM is expected to double in the Netherlands from 5,500 in 2000 to 10,400 in 2015[36]. The conclusion is that the increased risk of death in EEC is associated with the comorbid condition itself. The prognostic effects of co-morbidity on survival in EEC needs to taken into account along with the tumor related prognostic effects such as stage and grade. If we want to make more progress against EEC, we need to develop prevention strategies according to co-morbidity related to the obese epidemic. Furthermore, the EEC survivor group should be offered multi-behavioural lifestyle interventions after diagnosis.

Quality of life

Cancer treatment has three goals: to improve the cure rate, to lengthen survival time, and to improve quality of life (QOL). We learned that progress has been made on the first two goals, but at costs of long term sequelae of radiation treatment. Fortunately, PORTEC-1[1] results were implemented successfully with a reduction of overtreatment. In the southern part of the Netherlands, in the area of ECR, before the results of the PORTEC-1 trial were known, a trial was conducted[37] to test the hypothesis that less morbidity appears when radiotherapy (RT) could be withheld in the absence of lymph node metastasis. HRQoL was investigated on EEC cancer survivors in the area of the ECR. Women who underwent lymphadenectomy (LA+) reported higher lymphedema symptom scores and women who were treated with RT reported higher gastrointestinal symptom scores versus those who did not. Despite distinct symptom patterns among women who received LA or RT (LA+ or RT+), no clinically relevant differences in HRQL were observed when compared to women not receiving adjuvant therapy. Using LA to tailor adjuvant pelvic RT and prevent over-treatment in low-risk patients cannot be recommended. Here we see that side effects happen when we only focus on improving cure and prolonging survival. Fortunately, PORTEC-2[2] introduced vaginal brachy therapy (VBT), which has fewer toxic effects and the burden of visits to radiotherapy institution is reduced from 20 to only three sessions.
Another important reason to conduct HRQoL studies in cancer survivors is to improve survival after a successful cure. EEC survivors have been examined and unhealthy lifestyles were observed[38], thus putting them at risk for morbidity. As we realized with the increase

of low risk EEC, the number of endometrial cancer survivors will likely increase as well. The excellent work of the PROFILES registry[39] provides us with useful information about the health related quality of live. Chapter 4.2 described the health related quality of life (HRQoL) of endometrial cancer survivors in relation to co-morbidity and high BMI (≥ 30). Overweight or obese EEC survivors reported a poorer general health, more fatigue symptoms, lower physical functioning, more bodily pain, and more problems with work or daily activities. Patients in higher BMI categories reported more comorbidities. We conclude that a higher BMI has an important, mainly negative, contribution to the various HRQoL domains in early stage EEC survivors in addition to the contribution of comorbid conditions.

Future perspectives

In the literature, ample evidence has been given about the risk of endometrial cancer in relation to obesity. High BMI was significantly associated with markers of non-aggressive disease[40]. Recent genome-wide association studies (GWAS)[41;42] have identified multiple genetic markers, like genetic polymorphisms in the ADIPOQ gene[41;43;43] and fat mass and obesity-associated (FTO) gene[44], for the risk of endometrial cancer in obese women. The observed trend of increasing incidence of EEC due to the obesity epidemic (chapter 2.1) is an important health issue. In industrialized countries average body mass index is increasing[6] (figure 2). In figure 2 the mean BMI is pointed out till 2010. Data from CBS[15] statistics show that 37% of women in the Netherlands had a BMI between 25 and 30 and 11% has a BMI > 30 in 2011.

Thus, in the near future, prevention strategies in a selected group of obese women with aforementioned genetic markers should be developed. For example in the United Kingdom, screening of high risk patients without symptoms with transvaginal ultrasound showed at a cut-off of 6.75 mm a sensitivity of 84.3% (71.4-93.0) and specificity of 89.9% (89.3-90.5)[45]. Also it is important to educate bariatric surgeons to be aware of the risk factors of their obese female patients for endometrial carcinoma. At this moment we know from an extensive survey among bariatric surgeons in the USA that only 21% of the surgeons had ever referred a patient for endometrial evaluation[46].

Other preventive strategies recommended are interventions to reduce weight with diet and exercise. The health benefits of weight loss and a more active lifestyle are not only for endometrial cancer prevention but improvement in cardiovascular risk factors and reduced risk of developing diabetes and hypertension. In a recent review[47] only two of the 44 eligible studies presented intention-to-treat results and dropout rates were as high as 31–64%. Although many intervention studies are conducted in the USA[48], and recent intervention in Rotterdam by scientist at the Erasmus University[49] had promising results. Bariatric surgery in the severe obese patients is another strategy for weight loss with promising results, but at costs of complications and long term side effects[50]. Other strategies include endometrial protection in obese women with levonorgestrel

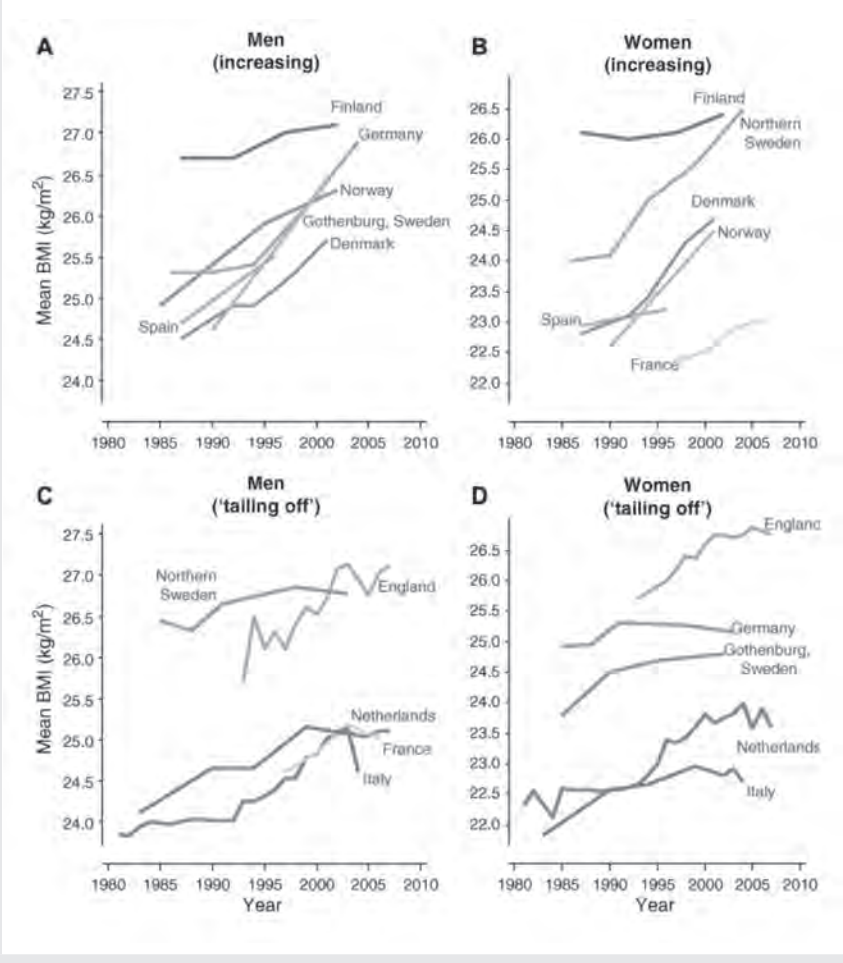

Figure 2 Epidemiology of body mass index in Europe. Trends in means of body mass index (BMI) distributions for 12 datasets across ten European countries shown for men and women. Trends are all increasing(25) (Renehan et al.).

intrauterine systems (LNG-IUS, such as Mirena). However, in a recent Cochrane review[48], insufficient evidence precluded recommendation of LNG-IUS to support its use as chemoprevention in women with obesity.

Together with the increase of low risk EEC, the number of endometrial cancer survivors will increase as well. The excellent work of the PROFILES registry provides us with useful

information about the health related quality of live. We learned from analysis of EEC cancer survivors with a high BMI that they suffer more fatigue symptoms and less vitality. In the USA, EEC survivors have been examined and unhealthy lifestyles were observed[38], thus putting them at risk for morbidity. In Cleveland, a successful pilot on EEC cancer survivors with severe obesity was conducted showing improvement in self-efficacy and eating behaviours[51]. Survivor groups should be offered multi-behavioural lifestyle interventions after diagnosis. One of the challenges and goals in future research should be to assess if interventions to decrease BMI and stimulate physical activity in obese EC survivors and to examine whether this will improve HRQoL.

Critical remarks on developing Quality indicators

The demand to develop quality indicators (QI) is increasing. Appropriate measures to be used for quality improvement are necessary, but complicated by the multidisciplinary nature of oncology. It requires the coordination of numerous providers across many specialties, further complicating data collection and quality assessment[52]. The fundamental goal of using QI is to improve health related outcomes. It is essential to choose a comprehensive set of measures that appropriately reflect quality and avoid inappropriate emphasis on any one part of the care process[53]. This is rapidly and progressively increasing new scientific areas of study. From the findings of this thesis, we recommend developing QI's to correct for co-morbidity in evaluation of survival and HRQoL. We conclude that co-morbidity is a prognostic factor for the survival of EEC and that obesity and diabetes specifically influence the HRQoL in EEC cancer survivors.

Reference List

(1) Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355(9213):1404-1411.

(2) Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010; 375(9717):816-823.

(3) Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002; 11(12):1531-1543.

(4) Ashizawa N, Yahata T, Quan J, Adachi S, Yoshihara K, Tanaka K. Serum leptin-adiponectin ratio and endometrial cancer risk in postmenopausal female subjects. Gynecol Oncol 2010; 119(1):65-69.

(5) Blokstra A, Vissink P, van der Schouw Y, Verschuren WMM. The Dutch were measured, 2009-2010. Audit of risk factors in the general population. RIVM Report 260152001/2011 2011.

(6) Renehan AG, Soerjomataram I, Tyson M, Egger M, Zwahlen M, Coebergh JW et al. Incident cancer burden attributable to excess body mass index in 30 European countries. Int J Cancer 2010; 126(3):692-702.

(7) Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. Eur J Cancer 2010; 46(14):2581-2592.

(8) Mourits MJ, Bijen CB, Arts HJ, ter Brugge HG, van der Sijde R, Paulsen L et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol 2010; 11(8):763-771.

(9) Fader AN, Seamon LG, Escobar PF, Frasure HE, Havrilesky LA, Zanotti KM et al. Minimally invasive surgery versus laparotomy in women with high grade endometrial cancer: a multi-site study performed at high volume cancer centers. Gynecol Oncol 2012; 126(2):180-185.

(10) Wright JD, Barrena Medel NI, Sehouli J, Fujiwara K, Herzog TJ. Contemporary management of endometrial cancer. Lancet 2012; 379(9823):1352-1360.

(11) Wright JD, Burke WM, Wilde ET, Lewin SN, Charles AS, Kim JH et al. Comparative Effectiveness of Robotic Versus Laparoscopic Hysterectomy for Endometrial Cancer. J Clin Oncol 2012.

(12) Subramaniam A, Kim KH, Bryant SA, Zhang B, Sikes C, Kimball KJ et al. A cohort study evaluating robotic versus laparotomy surgical outcomes of obese women with endometrial carcinoma. Gynecol Oncol 2011; 122(3):604-607.

(13) Frey MK, Ihnow SB, Worley MJ, Jr., Heyman KP, Kessler R, Slomovitz BM et al. Minimally invasive staging of endometrial cancer is feasible and safe in elderly women. J Minim Invasive Gynecol 2011; 18(2):200-204.

(14) Martinek IE, Haldar K, Tozzi R. Laparoscopic surgery for gynaecological cancers in obese women. Maturitas 2010; 65(4):320-324.

(15) Statistics Netherlands. http://statline.cbs.nl/StatWeb. Accessed January 2011.

(16) Karim-Kos HE, Kiemeney LA, Louwman MW, Coebergh JW, de VE. Progress against cancer in the Netherlands since the late 1980s: An epidemiological evaluation. Int J Cancer 2011.

(17) KWF. Cancer in the Netherlands till 2020. Signaleringscommissie Kanker 2011.

(18) Ueda SM, Kapp DS, Cheung MK, Shin JY, Osann K, Husain A et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008; 198(2):218-6.

(19) Boruta DM, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009; 115(1):142-153.

(20) Hendrickson MR, Longacre TA, Kempson RL. Uterine papillary serous carcinoma revisited. Gynecol Oncol 1994; 54(3):261-263.

(21) Trope C, Kristensen GB, Abeler VM. Clear-cell and papillary serous cancer: treatment options. Best Pract Res Clin Obstet Gynaecol 2001; 15(3):433-446.

(22) Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer 2006; 94(5):642-646.

(23) Amant F, Vergote I, Moerman P. The classification of a uterine sarcoma as 'high-grade endometrial stromal sarcoma' should be abandoned. Gynecol Oncol 2004; 95(2):412-413.
(24) Abeln EC, Smit VT, Wessels JW, de Leeuw WJ, Cornelisse CJ, Fleuren GJ. Molecular genetic evidence for the conversion hypothesis of the origin of malignant mixed mullerian tumours. J Pathol 1997; 183(4):424-431.
(25) Zelmanowicz A, Hildesheim A, Sherman ME, Sturgeon SR, Kurman RJ, Barrett RJ et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. Gynecol Oncol 1998; 69(3):253-257.
(26) Amant F, Vergote I. Bifunctional pathway of uterine carcinosarcomas. Hum Pathol 2003; 34(3):299.
(27) Mourits MJ, De Vries EG, Willemse PH, Ten Hoor KA, Hollema H, Van der Zee AG. Tamoxifen treatment and gynecologic side effects: a review. Obstet Gynecol 2001; 97(5 Pt 2):855-866.
(28) Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino J, Bernstein L et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol 2002; 20(11):2758-2760.
(29) Hoogendoorn WE, Hollema H, van Boven HH, Bergman E, de Leeuw-Mantel G, Platteel I et al. Prognosis of uterine corpus cancer after tamoxifen treatment for breast cancer. Breast Cancer Res Treat 2008; 112(1):99-108.
(30) Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 2000; 356(9233):881-887.
(31) Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993-1996. J Clin Epidemiol 1999; 52(12):1131-1136.
(32) Vulto AJ, Lemmens VE, Louwman MW, Janssen-Heijnen ML, Poortmans PH, Lybeert ML et al. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. Cancer 2006; 106(12):2734-2742.
(33) Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer 2011; 47(10):1504-1510.
(34) Dossus L, Kaaks R. Nutrition, metabolic factors and cancer risk. Best Practice & Research Clinical Endocrinology & Metabolism 2008; 22(4):551-571.
(35) Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007; 50(7):1365-1374.
(36) Cancer in the Netherlands. Trends, prognoses en implications for healthcare. Amsterdam. Signalling Committee Cancer of the Dutch Cancer Society 2004.
(37) Zuurendonk LD, Smit RA, Mol BW, Feijen HW, de GJ, Sykora D et al. Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. Eur J Surg Oncol 2006; 32(4):450-454.
(38) von Gruenigen VE, Waggoner SE, Frasure HE, Kavanagh MB, Janata JW, Rose PG et al. Lifestyle challenges in endometrial cancer survivorship. Obstet Gynecol 2011; 117(1):93-100.
(39) van de Poll-Franse LV, Horevoorts N, van EM, Denollet J, Roukema JA, Aaronson NK et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer 2011; 47(14):2188-2194.
(40) Mauland KK, Trovik J, Wik E, Raeder MB, Njolstad TS, Stefansson IM et al. High BMI is significantly associated with positive progesterone receptor status and clinico-pathological markers for non-aggressive disease in endometrial cancer. Br J Cancer 2011; 104(6):921-926.
(41) Delahanty RJ, Beeghly-Fadiel A, Xiang YB, Long J, Cai Q, Wen W et al. Association of obesity-related genetic variants with endometrial cancer risk: a report from the Shanghai Endometrial Cancer Genetics Study. Am J Epidemiol 2011; 174(10):1115-1126.
(42) Long J, Zheng W, Xiang YB, Lose F, Thompson D, Tomlinson I et al. Genome-wide association study identifies a possible susceptibility locus for endometrial cancer. Cancer Epidemiol Biomarkers Prev 2012; 21(6):980-987.
(43) Chen X, Xiang YB, Long JR, Cai H, Cai Q, Cheng J et al. Genetic polymorphisms in obesity-related genes and endometrial cancer risk. Cancer 2012; 118(13):3356-3364.

(44) Zhang Z, Zhou D, Lai Y, Liu Y, Tao X, Wang Q et al. Estrogen induces endometrial cancer cell proliferation and invasion by regulating the fat mass and obesity-associated gene via PI3K/AKT and MAPK signaling pathways. Cancer Lett 2012; 319(1):89-97.
(45) Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol 2011; 12(1):38-48.
(46) Winfree LE, Henretta MS, Hallowell PT, Modesitt SC. Pre-operative gynecologic evaluation of bariatric surgery patients: improving cancer detection in a high-risk population. J Am Coll Surg 2010; 211(2):256-262.
(47) Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, Williamson D et al. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring) 2006; 14(5):737-752.
(48) Wan YL, Holland C. The efficacy of levonorgestrel intrauterine systems for endometrial protection: a systematic review. Climacteric 2011; 14(6):622-632.
(49) de Vos BC, Runhaar J, Bierma-Zeinstra SM. Effectiveness of a tailor-made weight loss intervention in primary care. Eur J Nutr 2013.
(50) Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004; 351(26):2683-2693.
(51) von Gruenigen V, Frasure H, Kavanagh MB, Janata J, Waggoner S, Rose P et al. Survivors of uterine cancer empowered by exercise and healthy diet (SUCCEED): a randomized controlled trial. Gynecol Oncol 2012; 125(3):699-704.
(52) Albert JM, Das P. Quality assessment in oncology. Int J Radiat Oncol Biol Phys 2012; 83(3):773-781.
(53) Rubin HR, Pronovost P, Diette GB. The advantages and disadvantages of process-based measures of health care quality. Int J Qual Health Care 2001; 13(6):469-474.

Summary

In this thesis trends in incidence and outcome of corpus uteri malignancies in The Netherlands are described since the 1980's. Several registry-based studies are presented with an evaluation of variation in incidence and outcome.
Chapter 1 provides a general introduction to the thesis, and provides the aims of the study. An overview of the literature on corpus uteri malignancies also is presented. In chapter 2 of the thesis, the oncologic point of view is presented with a clinical reality based only on newly diagnosed cases according to stage and histological type, treatment, survival and mortality. Subsequently, potential implications of different trend findings for clinical practice are discussed. In the second part of the thesis, chapter 3, the approach to life expectancy for the majority of patients with endometrioid endometrial carcinomas (EEC) is put into perspective of patient characteristics like age, concomitant diseases such as diabetes mellitus. Chapter 4 presents large population based studies on the health related quality of life of survivors of EEC. Chapter 5 discusses the question if we can improve the survival and decrease the mortality in unfavourable corpus uteri malignancies. Specifically, section 5.2 presents the main findings on tumour and patient characteristics including an overall view of the impact of trends in life expectancy on policy towards diagnosis and treatment of corpus uteri malignancy.

The aims of this thesis were to:

1 Provide detailed information on the epidemic of corpus uterine malignancies in The Netherlands by presenting age-,stage- and histology-specific trends of incidence, relative survival, effects on survival of changes in treatment and trends in mortality from uterine malignancies between 1989-2009, to be able to assess the progress against uterine malignancies in the past decades. Data used were extracted from the Netherlands Cancer Registry (NCR).
2 Explore the influence of patient characteristics like co-morbidity, diabetes mellitus and age on treatment and survival and evaluation of the adherence to national Dutch guidelines. Data used were extracted from the Eindhoven Cancer Registration (ECR) and Registration Oncologic Gynecologic (ROGY).
3 Presenting a dual population based study on the health related quality of life (HRQoL) of the endometrial cancer survivors for evaluation of long-term sequelae of cancer management and evaluate physical and psychosocial care (needs) of cancer survivors. Data were taken from PROFILES (Patient Reported Outcome Following Initial Treatment and Long term Evaluation of Survivorship) registry.
4 Present and discuss a point of view on how the survival of women with grade 3 EEC, advanced stage EEC, and NEEC can be improved and how mortality due to malignancies of the uterine body can be reduced.

Chapter 2. Trends in corpus uteri malignancies between 1989-2009

A total of 32,332 women with a newly diagnosed corpus uteri malignancy were registered in the NCR between 1989 and 2009. The majority of the corpus uteri malignancies (80%) are EEC. The less common types of corpus uteri malignancies, serous adenocarcinoma, clearcell carcinoma, and carcinosarcoma are classified as non-endometrioid endometrial carcinomas (NEEC) and concern 15% of the corpus uteri malignancies. A third classification is the mesenchymal corpus uteri malignancies or the sarcomas, which comprise the minority with 4%.

Trends in EEC

Incidence of EEC rose significantly from 11/100,000 to 15/100,000, being most pronounced in women with FIGO stage IB and in the group with grade 1&2 tumours ($P < 0.05$). These results are based on a descriptive population based study of the increased incidence and improved survival in EEC diagnosed since 1989 in the Netherlands. The strongest association for the enhanced EEC risk is obesity. Coinciding with the increased incidence, the 5-year relative survival during 2005-09 increased, especially for patients aged 60-74 years, in women with FIGO stage I, and in histology group grade 1&2, at 87%, 94% and 93%, respectively. Progress against EEC has been less than was assumed previously, due to the increasing incidence and because, although survival improved, mortality proportionally decreased only slightly.

Trends in treatment

A reduction in adjuvant radiotherapy occurred based on increasingly evidence-based treatments of patients with EEC resulting in similar survival in the Netherlands between 1994-2009. These results are based on trends in treatment of EEC in a descriptive population based study. Analysis included grade, stage and age, and the impact of changes in treatment strategies on survival. Multivariable relative survival analyses were performed to estimate relative excess risk (RER) of dying for the periods of diagnosis adjusted for follow-up interval and stratified for FIGO stage. Between 1994 and 2009, a total of 20,386 women were diagnosed with EEC, the majority of women having stage IB en IC. Over time a significant decrease in adjuvant radiotherapy for stage I in age group 45-59 years of age was observed. Additionally, a significant increase in adjuvant radiotherapy occurred in stage IC for age groups of 60 years and older. Since 2007 data show a trend towards more adjuvant radiotherapy in stage I EEC for age group of 80+. The 5-year relative survival did not change over time for stage I and II. The known prognostic factors like age and grade have a significant influence on the RER and on survival. The successful implementation of the results of RCT PORTEC-1 led to reduction of overtreatment and the introduction of the results of PORTEC-2 to reduction of under treatment in the elderly patients by replacing external beam radiotherapy by vaginal brachytherapy in low to intermediate risk EEC.

Trends in uncommon corpus uterine malignancies

For the period 1989-2008, the incidence of corpus uteri malignancies in the Netherlands increased from 159 to 177 per 1,000,000 person-years (p-y), mainly owing to the rise in endometrioid adenocarcinomas from 106 to 144 per 1,000,000 p-y. In contrast, the incidence of uncommon epithelial endometrial carcinomas (UEECs) decreased from 30 to 13 per 1,000,000 p-y, although carcinosarcomas increased slightly from 5.1 to 6.9 per 1,000,000 p-y. All common and uncommon malignancies of the corpus uteri registered in the nationwide population-based NCR during 1989-2008 were included (n = 30,960) in the analysis. The histological subtypes were described according to the Blaustein classification system. Age-standardized incidence for 1989-2008 was calculated per 1,000,000 p-y.

Furthermore, a remarkable shift in incidence of endometrial stromal cell sarcomas (ESS) was observed from high-grade ESSs to low-grade ESSs after 2003. The 5-year relative survival for patients with UEEC decreased from 72% to 54% and for patients with serous adenocarcinoma from 73% to 51%. Coinciding with an increase in the incidence of common adenocarcinoma of the corpus uteri, there was a decline in uncommon adenocarcinomas and more or less a stable incidence of sarcomas and carcinosarcomas.

The decrease in UEEC tumors consisted largely of fewer serous carcinomas, possibly and likely reflecting a more precise histopathological classification of villoglandular tumours. Unfortunately, relative survival for patients with UEEC, sarcomas, and carcinosarcomas did not improve over the study period, indicating a need for more research on treatment strategies for this group of patients.

Chapter 3. Role of co-morbidity

EEC is a cancer with a good prognosis and in these cancer types relative survival statistics have a limited clinical relevance, because relative survival and observed survival differ. The observed survival reflects the effects of both non-cancer and cancer-related causes of death. Therefore, this thesis explored the influence of patient characteristics like age and co-morbidity on treatment and survival. Co-morbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis, for example: cardiovascular disease, previous malignancy and diabetes mellitus.

Endometrial cancer and co-morbidity

Endometrial cancer (EC) in the south of the Netherlands between 1995 and 2008 occurred more frequently amongst women over 60 years of age, who often also suffer from co-morbidity. These results are based on adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity. Whereas treatment guidelines are derived from clinical trials that usually exclude older EC patients, these guidelines are also applied to these patients. We assessed the independent influence of age and co-morbidity on treatment modalities and survival of patients with stage I EC in

everyday clinical practice, thereby also examining the implementation of Dutch guidelines on treatment, since 2000. A total of 2099 stage I EC patients diagnosed between 1995 and 2008 registered in the ECR (Eindhoven Cancer Registry) were included for analysis of the influence of age and co-morbidity on treatment and survival. For co-morbidity we used a modified version of Charlson's list, uniquely recorded in the ECR since 1983. A subgroup analysis was performed for patients who should have received adjuvant radiotherapy based on the risk factors suggested in the Dutch guidelines of 2000. We considered five periods (1995–97; 1989–2000; 2001–03; 2004–06; 2007–08). Having two or more co-morbid conditions resulted in a significant reduction of receiving adjuvant radiotherapy (Odds Ratio: 0.6, 95% Confidence Interval (95% CI): 0.3–1.0)) but receiving adjuvant radiotherapy did not appear to improve survival. After adjustment for age, tumour stage, tumour grade, period of diagnosis and treatment, co-morbidity increased the risk of death, especially diabetes (Hazard Ratio (HR) for mortality: 2.9,95%CI: 2.2–4.0), a previous cancer (HR: 2.6, 95%CI: 1.9–3.7) and cardiovascular disease (HR: 2.3, 95%CI: 1.7–3.2). The combination of two or more co-morbid conditions resulted in a HR of 3.0 (95%CI: 2.2–3.9).
Co-morbidity decreased the likelihood of receiving adjuvant radiotherapy in patients with stage I EC qualified to undergo this treatment according to the Dutch guidelines of 2000. Whereas adjuvant radiotherapy did not seem to affect survival in those patients, co-morbidity significantly did.

Role of Diabetes Mellitus

To investigate the effect of diabetes on endometrial cancer recurrence and survival, we analyzed the influence of diabetes mellitus (DM) on cancer stage at diagnosis, cancer recurrence, and survival of endometrioid endometrial cancer (EEC) patients and the influence of the treatment of EC on glycaemic control, treatment, and complications of DM. In this retrospective cohort study all 1,644 patients with EC newly diagnosed in 2000-2008 and recorded in the population-based Eindhoven Cancer Registry (ECR) were included. In addition, a sub cohort was selected for additional analyses, including 193 EEC patients with DM and a matched sample of 195 EEC patients without DM. Patients with FIGO stage IV as well as non-endometrioid histology were excluded. EEC patients with DM had a significantly higher age (69 years vs. 64 years), higher FIGO stages, higher body mass index (BMI) (34 kg/m^2 vs. 30 kg/m^2), lower socioeconomic status (SES), and more comorbidities compared to EEC patients without DM. In contrast, EEC was not significantly associated with changes in DM characteristics over time. The 5-year overall survival rate for EEC patients with DM was significantly lower than for EEC patients without DM (68% vs. 84%), after adjusting for age, stage, period of diagnosis, cardiovascular disease, and treatment. This statistically significant effect of DM on overall mortality persisted (HR 1.4, 95% CI: 1.0-1.8)throughout the study period. On the contrary, for EEC-specific mortality (n=388) no statistically significant effect of DM was observed after adjustment for FIGO stage (HR = 1.7, 95% CI: 0.7-3.9). EEC patients with DM compared to those without had

worse patient characteristics, similar recurrence rates, a higher FIGO stage, and overall mortality.

Chapter 4. Quality of Life

The actual benefits from progress against uterine malignancies need to be analysed in relation to the long-term sequelae of cancer management and the health related quality of life (HRQoL) of cancer survivors. The number of long-term EEC survivors will increase substantially, 3-5% per year. Data from the PROFILES (Patient Reported Outcomes Following Initial Treatment and Long term Evaluation of Survivorship) registry from 1999-2007 were used for two health related analyses: 1. to evaluate side effects of radiotherapy and lymph adenectomy, and 2. to evaluate the influence of high BMI in endometrial cancer survivors on HRQoL.

Side effects of Radiotherapy (RT) and Lymph Adenectomy

A large population-based study was conducted on HRQoL and symptoms after pelvic lymphadenectomy or RT versus no adjuvant regional treatment in early-stage endometrial carcinoma. The hypothesis that less morbidity when RT could be withheld in the absence of lymph node metastasis was examined by evaluation of health related quality of life (HRQL) in endometrial cancer survivors that received routine pelvic LA without RT compared to no LA, but RT in the presence of risk factors. Stage I–II endometrial cancer survivors diagnosed between 1999 and 2007 were selected from the ECR. Survivors completed the SF-36 and the EORTC-QLQ-EN24. ANCOVA and multiple linear regression analyses were applied. A total of 742 (77%) of the endometrial cancer survivors returned a completed questionnaire. Among those who completed the questionnaire, 377 (51%) had received no LA nor RT (LA–RT–), 198 (27%) had received LA but no RT (LA+RT–), 153 (21%) RT and no LA (LA–RT+), and 14 patients (2%) had received both (LA+RT+). LA+ women reported higher lymphedema symptom scores (25 vs. 20, p=0.04). Women with RT+ had higher gastrointestinal symptom scores vs. those RT– (23 vs. 16, p=0.04). HRQL scales were comparable between all four treatment groups. Despite distinct symptom patterns among women who received LA or RT(LA+ or RT+), no clinically relevant differences in HRQL were observed when compared to women who did not receive adjuvant therapy. The use of LA to tailor adjuvant pelvic RT to prevent over-treatment in low-risk patients cannot be recommended.

Influence of high BMI in endometrial cancer survivors on HRQoL

The association of BMI and other comorbidities on quality of life and fatigue of endometrial cancer survivors was examined in a population-based, cross-sectional survey among endometrial cancer (EC) survivors diagnosed between 1999 and 2007 sampled from the Eindhoven Cancer Registry. The HRQoL (SF-36), EC specific QoL (EORTC-QLQ-EN24), and fatigue (FAS) questionnaire were completed by 742 EC survivors (77%). Of all EC women,

478 (64.4%) were overweight or obese (BMI ≥ 25). BMI was associated with physical function (p< 0.0001), vitality (p< 0.05), lymphedema (p<0.0001), sexual/vaginal problems (p<0.0001), taste change (p<0.05), and fatigue (p<0.05). BMI showed significant increase in explained variance in domains of physical function (p<0.0001), role physical (p<0.05), bodily pain (p<0.01), vitality (p<0.01), and role emotional (p<0.05). BMI also caused an increase in explained variance within endometrial specific problems, i.e. lymph oedema (p<0.0001), sexual/vaginal problems (p<0.01), back/pelvic pain (p<0.05), and fatigue (p<0.01). The results of this study suggest that BMI has an additional impact on fatigue and HRQoL domains in EC survivors independent of other comorbidities. Although other comorbidities combined have a greater additional effect on HRQoL than BMI alone, BMI should be included in research among EC patients along with other comorbidities.

Chapter 5. General discussion

First, this chapter addresses the survival gap between patients of ≥75 years of age and patients < 60 years of age as observed in this thesis . Survival did not improve in stage III EEC and/or in high grade EEC, both occur more often in the elderly patients. Although an increase is seen in chemotherapy treatment in the advanced stages, this had no influence on the RER of dying. Older women more often have a tumour with bad prognoses as the median age we observed was 68 years in NEEC, 71 years for clearcell, and 75 years for the very rare tumours like neuroendocrine and mixed tumors. Five year relative survival for NEEC during 2004-2008 was 60% and declined to 40% for women of ≥75 years. Also carcinosarcoma occurred more frequently in older women and had a poor prognosis especially for women of ≥75 year. Improvement in health status in the elderly patients is dependent on many other parameters (i.e. multi morbidity, dependence on functional status and frailty) beside longer survival. Improvement in treatment of comorbidities can result in better relative survival.

Second, this chapter 5.1 discusses the question: "Can we improve survival and decrease the mortality in the unfavourable types of uterine malignancies?" In order to improve survival for women with EC and decrease their mortality, treatment strategies have been proposed in addition to the standard surgery and RT, such as extensive cytoreductive surgery and adjuvant chemotherapy. These strategies, however, have not yet been proven successful in randomized trials. The unfavourable tumour characteristics of EC and NEEC mainly occur in patients aged ≥75, who frequently suffer from multimorbidity and who are more vulnerable. The survival and mortality is clearly influenced by patient characteristics. Aspirations to improve survival should be put into perspective for this group of patients because, due to factors such as the burden of treatment and convalescence, priority for them does not lie with longevity, the impact on self-reliance, and their perspective on life, but rather with symptom management. Elderly patients, who are fit and vital according to a geriatric assessment, appear to cope well with extensive surgery, preferably with minimally invasive techniques, as well as adjuvant treatment with

radiotherapy and chemotherapy. It is advisable that these fit and vital elderly patients be involved in clinical trials more than has been the case to date, to arrive at an evidence-based choice for a meaningful treatment strategy.

The second part , 5.2 of the general discussion reveals that life expectancy for the majority of patients with EEC is related to patient characteristics including age, concomitant diseases, such as diabetes mellitus, and a high body mass index (BMI). Quality of care and quality of life considerations are also discussed. Finally, recommendations are provided for prevention strategies and for future research.

Samenvatting

Hoofdstuk 1 bevat een algemene inleiding over de achtergrond van corpus uteri maligniteiten en biedt een overzicht van de literatuur over dit onderwerp. Daarna komt aan de orde de opbouw van het onderzoek naar trends in incidentie en uitkomsten van corpus uteri maligniteiten. Hoofdstuk 2 gaat vanuit een oncologische visie in op de klinische realiteit aan de hand van een indeling naar histologie en stadium, waarbij incidentie, behandeling, survival en mortaliteit van corpus uteri maligniteiten in de periode 1989-2009 worden beschreven. Daarbij is gebruik gemaakt van de Nederlandse Kanker Registratie (NKR). Vervolgens worden besproken de gevolgen die de gevonden trends hebben voor de klinische praktijk. Hoofdstuk 3 gaat in op de levensverwachting van vrouwen met een endometrioid endometrium carcinoom (EEC), de meerderheid van patiënten met een corpus uteri maligniteit. Die levensverwachting wordt beschreven op basis van patiënt-karakteristieken zoals leeftijd en comorbiditeit, bijvoorbeeld diabetes mellitus (DM). In paragraaf 3. 2 wordt dieper ingegaan op de relatie tussen EEC en DM. Hoofdstuk 4 bevat twee populatie-studies over kwaliteit van leven bij vrouwen die een endometrium carcinoom overleefden. In hoofdstuk 5 komt aan de orde de vraag of bij de ongunstige types van het endometrium carcinoom de overleving kan verbeteren en de mortaliteit kan worden teruggedrongen. Verder worden de belangrijkste bevindingen omtrent tumor- en patiëntkarakteristieken behandeld en wordt een visie op levensverwachting besproken in relatie tot de betekenis hiervan voor diagnostiek en behandeling van corpus uteri maligniteiten.

Dit proefschrift beoogt:

1. Het geven van gedetailleerde informatie over de epidemiologie van corpus uteri maligniteiten in Nederland, aan de hand van een beschrijving van incidentie en relatieve overleving ingedeeld naar leeftijd, periode van diagnose, histologie en stadium. Daarnaast volgt een analyse van verandering in behandeling op de overleving en een beschrijving van de effecten op de mortaliteit, waarbij wordt nagegaan of vooruitgang is bereikt. De beschreven periode is 1989-2009, waarbij gebruik is gemaakt van data van de NKR.
2. Het analyseren van de invloed van patiëntkarakteristieken zoals leeftijd, comorbiditeit, bijvoorbeeld diabetes mellitus, op behandeling en overleving in geval van endometriumcarcinoom. Daarbij is tevens een evaluatie uitgevoerd van de mate waarin de Nederlandse richtlijnen worden nageleefd. Hierbij is gebruik gemaakt van data van de Eindhovense Kanker Registratie (EKR) en van het web-based registratieprogramma voor oncologische gynaecologie (ROGY).
3. Het in kaart brengen van populatie-studies over kwaliteit van leven bij vrouwen die het endometrium carcinoom hebben overleefd. Daarbij zijn de lange termijneffecten van kankerbehandeling, zowel in fysiek als in psychisch opzicht, geëvalueerd. Dit

onderdeel is gebaseerd op data van de Profiles registratie (Patient reported Outcome Following initial Treatment and Long term Survivorship).

4. Bijdragen aan beantwoording van de vraag hoe de overleving van vrouwen met een graad 3 endometrium carcinoom, een gevorderd endometriumcarcinoom of een ongunstig type endometriumcarcinoom, varianten die vaker voorkomen bij oudere en kwetsbare patiënten, valt te verbeteren en de sterfte aan corpus uteri maligniteiten kan worden teruggedrongen.

Hoofdstuk 2. Trends in corpus uteri maligniteiten in de periode van 1989-2009

In de periode 1989-2009 zijn in totaal 32.332 vrouwen met een corpus uteri maligniteit gediagnosticeerd. Van de patiënten met de diagnose corpus uteri maligniteit blijkt 80% te lijden aan een endometrioid endometrium carcinoom (EEC). De minder voorkomende varianten, zoals het sereus adenocarcinoom, het heldercellig carcinoom en het carcinosarcoom - ook wel de niet endometrioide carcinomen (NEEC) genoemd- betreffen 15% van de corpus uteri maligniteiten. In ongeveer 4% van de gevallen gaat het om mesenchymale tumoren, zoals sarcomen.

Trends in EEC

De incidentie van EEC nam in de onderzoeksperiode significant toe van (11/100.000 tot 15/100.000). Het meest uitgesproken was dit het geval bij vrouwen met FIGO stage IB (< ½ ingroei in het myometrium) en in de groep met graad 1&2 tumoren ($P < 0.05$). De incidentie van de gevorderde stadia III en IV is niet gestegen en verhoudingsgewijs ten opzichte van de vroege stadia zelfs afgenomen. Deze resultaten zijn gebaseerd op een beschrijvende populatiestudie waarin de gestegen incidentie en de verbeterde overleving in EEC sinds 1989 wordt weergegeven. De relatieve vijfjaars overleving nam in deze periode toe, met name bij vrouwen van 60-74 jaar (naar 87%), bij vrouwen met FIGO stadium I (naar 94%) en bij vrouwen met graad 1&2 tumoren (naar 93%). De progressie in de bestrijding van EEC was echter minder dan verwacht, omdat de mortaliteit verhoudingsgewijs slechts weinig afnam, ondanks het feit dat de overleving verbeterde.

Trends in behandeling

In de onderzoeksperiode trad een significante daling op van het aantal vrouwen dat werd behandeld met adjuvante radiotherapie. De vijfjaars overleving veranderde in deze periode niet voor stadium I en II . Deze resultaten zijn gebaseerd op een beschrijvende populatiestudie naar trends in behandeling van EEC, waarbij data uit de NKR zijn gebruikt. De analyse van de invloed van behandeling op de overleving is uitgevoerd met een correctie voor leeftijd, gradering en stadium van de tumor. Een multivariabele analyse is uitgevoerd voor de relatieve overleving met een berekening van het relatieve extra risico op overlijden (RER). Een totaal aantal van 20.386 vrouwen is in deze periode gediagnosticeerd met EEC. De meerderheid daarvan had een stadium IA, IB en IC (FIGO 1988). In de

leeftijdsgroep onder 60 jaar en bij een myometrium invasie < 50% (FIGO 1988 IA en IB) is een significante stijging van het geven van adjuvante radiotherapie vastgesteld voor stadium IC (≥50% myometrium invasie) EEC. Daarnaast trad vanaf 2007 een stijging op van adjuvante radiotherapie bij vrouwen van 80 jaar en ouder. De belangrijkste factoren die de overleving beïnvloedden zijn leeftijd en gradering van de tumor. Deze factoren hadden een significante invloed op de RER. Deze analyse laat overtuigend zien dat in Nederland de resultaten van de gerandomiseerde trial PORTEC 1 voortvarend zijn ingevoerd en hebben geleid tot een reductie van de aanvankelijke overbehandeling in de groep vrouwen onder 60 jaar. Waarschijnlijk is door de resultaten van de vervolgstudie PORTEC-2 (2007) de onderbehandeling in de leeftijdsgroep van oudere vrouwen gecorrigeerd, als gevolg van vervanging van uitwendige radiotherapie door vaginale brachytherapie in gevallen van laag en matig risico EEC.

Trends in zeldzame corpus uteri maligniteiten

In periode 1989-2008 steeg de incidentie van het aantal corpus uteri maligniteiten in Nederland van 159 per 1.000.000 vrouwen per jaar naar 177 per 1.000.000 vrouwen per jaar. Deze toename is toe te schrijven aan de stijging van de incidentie van Endometrioide Endometrium Carcinoom (EEC), hetgeen het meest voorkomende type baarmoederkanker is. De incidentie van uncommon epitheliale endometrium carcinomen (UEEC), ook wel non-endometrioide tumoren genoemd, daalde in deze periode van 30 per 1.000.000 naar 13 per 1.000.000. Het carcinosarcoom, voorheen Maligne Mixed Müllerian tumor (MMMT), steeg in geringe mate van 5.1 naar 6.9 per 1.000.000.

In hoofdstuk 2.3 wordt ingegaan op de trends in incidentie en survival van zeldzame maligniteiten van corpus uteri in Nederland. Onder zeldzame tumoren worden verstaan: tumoren die minder dan 6 per 100.000 voorkomen. Een onderverdeling van de zeldzame corpus uteri maligniteiten is gemaakt op basis van de WHO- indeling, aangepast volgens de meer gedetailleerde indeling van Blaustein. De data werden verkregen uit de NKR. In verband met de geringe incidentie van sommige tumoren is gekozen voor een weergave van de incidentie in aantallen per 1.000.000 vrouwen per jaar, gecorrigeerd voor de leeftijdsverdeling in de Europese bevolking ook wel European standardised Ratio (ESR) genoemd. De leeftijd van de vrouwen met zeldzamere uterus maligniteiten ligt tussen 48-79 jaar. De grootste daling is vastgesteld in de groep van de papillair sereuze tumoren; de ESR daalde van 22 (1989-93) naar 7 per 1.000.000 (2004-08). Hoewel de incidentie voor sarcomen niet veel veranderde, valt vanaf 2003 wel een duidelijke verschuiving te constateren in de groep met een endometriaal stromacel sarcoom (ESS) van het hoog gradige ESS naar het laag gradige ESS. De relatieve vijfjaars overleving in de UEEC daalde van 72 % (1989-93) tot 54% (2004-08); voor papillair sereus adenocarcinoom van 73% (1989-93) naar 51 % (2004-08). De afname in incidentie van de UEEC kan met name worden verklaard door de daling van de incidentie van het papillair sereus adenocarcinoom. De belangrijkste reden voor deze daling is gelegen in veranderingen op het gebied van de

pathologische anatomie. Voor 1994 werd een variant van het endometrioide EC, namelijk de villoglandulaire differentiatie, wel verward met het meer maligne papillair sereuze adenocarcinoom, tegenwoordig ook wel kortweg sereus adenocarcinoom genoemd. Deze nieuwe inzichten, tezamen met de ontwikkeling van de immunohistochemie, hebben het diagnostisch proces verbeterd. De daling van de overleving bij het sereuze adenocarcinoom die zich na 1994 heeft voorgedaan kan ook door deze verandering worden verklaard. Helaas moeten wij concluderen dat de vijfjaars overleving van vrouwen met UEEC en carcinosarcomen laag is en niet verbeterde in de onderzoeksperiode, met uitzondering van het laag gradige ESS.

Hoofdstuk 3. De rol van comorbiditeit.

Het endometrioid endometriumcarcinoom is veelal een variant van corpus uteri maligniteiten met een goede prognose. In het algemeen geldt dat bij varianten van kanker met een goede prognose, anders dan bij letale vormen van kanker, de relatieve survival een minder goede uitkomstmaat is. Bij kanker met een goede prognose treedt vaker een verschil op tussen relatieve overleving en geobserveerde overleving. Dit doet zich vaker voor naarmate de leeftijd vordert. De geobserveerde overleving betreft zowel sterfte aan kanker als sterfte aan bijkomende ziektes. In dit kader is een analyse uitgevoerd van de invloed van patiënt karakteristieken, zoals leeftijd en comorbiditeit, op de behandeling en overleving van EEC. Comorbiditeit wordt gedefinieerd als de ziektes die een patiënte heeft ten tijde van de diagnose EC en die een negatieve invloed hebben op de levensverwachting. Voorbeelden van comorbiditeiten zijn hart- en vaatziekten, hypertensie, een eerdere maligniteit in de voorgeschiedenis en diabetes mellitus.

Endometrium carcinoom en comorbiditeit

In deze studie zijn alle patiënten geincludeerd die, blijkens de Eindhovense Kanker Registratie (EKR), in de periode 1995 - 2008 werden gediagnosticeerd met een EC Figo stadium I. Het ging daarbij om 2099 vrouwen. De EKR registreert alle nieuwe patiënten die in deze regio, die 2.4 miljoen inwoners omvat, gediagnosticeerd worden met een vorm van kanker. Sinds 1983 registreert de EKR ook de comorbiditeit van patiënten op basis van een gemodificeerde lijst die is gebaseerd op de Charlson's comorbidity index. Het merendeel van de vrouwen (66%) was 60 jaar of ouder. In 59% van de gevallen was sprake van comorbiditeit. Een subgroep analyse is uitgevoerd bij 444 vrouwen, om na te gaan of comorbiditeit invloed had op de naleving van de landelijke richtlijn voor adjuvante radiotherapie, omdat is gebleken dat in trials oudere patiënten met comorbiditeit vaak worden geëxcludeerd. De landelijke richtlijn is gebaseerd op de resultaten van de PORTEC-1 trial, die in 2000 zijn gepubliceerd en betreft de regel twee van drie. Wanneer twee van drie risico factoren positief zijn (leeftijd ≥60, > ½ myometriuminvasie, graad 3) wordt adjuvante radiotherapie aanbevolen. Voor de multivariate survival analyse in verband met de kans op mortaliteit waren de gegevens van 1770 patiënten compleet. De

kans op overlijden voor patiënten met twee of meer comorbiditeiten blijkt significant hoger; de hazard ratio (HR) tot overlijden is 3.0 (95% CI: 2.2-3.9) vergeleken met patiënten zonder comorbiditeit. De vijfjaars overleving bedraagt 73% voor patiënten met twee of meer comorbiditeiten, versus 91% voor patiënten zonder comorbiditeit. Patienten van 60 jaar en ouder hebben een significant hoger risico op overlijden HR 3.0 (95% CI: 2.1-4.2) vergeleken met patiënten jonger dan 60 jaar. Bij patiënten met specifieke comorbiditeiten is het mortaliteitsrisico significant hoger ten opzichte van patiënten zonder comorbiditeit. Voor diabetes is de HR 2.9 (95% CI: 2.2-4.0), voor een eerdere maligniteit is dit 2.6 (95% CI: 1.9-3.7) en voor cardiovasculaire aandoeningen bedraagt de HR 2.3 (95% CI: 1.7-3.2). Het al dan niet hebben ontvangen van radiotherapie blijkt geen invloed te hebben op mortaliteit; de HR is 1.0 (95% CI: 0.7-1.3).
De conclusie is dat de invoering van de landelijke richtlijn voor adjuvante radiotherapie heeft geleid tot een afname van het aantal patiënten dat adjuvante radiotherapie krijgt. Het aantal patiënten dat geen adjuvante radiotherapie ontvangt, terwijl daarvoor wel een indicatie bestaat, is in de loop van de onderzoeksperiode stabiel gebleven, hetgeen mogelijk samenhangt met comorbiditeit. De kans op overlijden is significant hoger bij patiënten van 60 jaar en ouder, bij twee of meer comorbiditeiten, bij diabetes, in geval van een eerdere maligniteit in de voorgeschiedenis en bij cardiovasculaire aandoeningen. Op basis van deze populatiestudie kan worden vastgesteld dat comorbiditeit geen invloed heeft op het besluit tot uitvoeren van een hysterectomie bij patiënten met EC stadium I. Wel blijken patiënten met twee of meer comorbiditeiten significant vaker geen adjuvante radiotherapie te ontvangen. Adjuvante radiotherapie blijkt geen invloed te hebben op de overleving, maar het hebben van comorbiditeit heeft wel een significante invloed op het risico van overlijden.

De rol van diabetes mellitus

Om het effect te van diabetes mellitus (DM) op de prognose van vrouwen met een EEC beter te begrijpen, is een onderzoek uitgevoerd naar de invloed van DM op het stadium van EEC ten tijde van het stellen van die diagnose en de invloed daarvan op de recidiefkans en de overleving. Daarnaast is nagegaan wat het effect is van EEC op glycaemische controle bij DM- patiënten, op behandeling van DM en op complicaties bij DM. In deze retrospectieve cohort studie zijn aan de hand van de EKR de nieuw geregistreerde patiënten met EEC geincludeerd tussen 2000 en 2008. Het gaat daarbij om 1.644 vrouwen. Van hen hadden 255 (16%) patiënten DM. Er is een subgroep van 193 patiënten samengesteld waarvan de gegevens compleet waren. Vervolgens is een match sample van 195 patiënten met EEC geselecteerd zonder DM. Patienten met FIGO stadium IV en patiënten met niet-endometrioide EEC zijn wegens het kleine aantal geëxcludeerd. EEC -patiënten met DM hebben in vergelijking met EEC- patiënten zonder DM een significant hogere leeftijd (69 versus 64 jaar), hogere FIGO stadia bij diagnose, een hogere body mass index (BMI) (34 versus 30 kg/m^2), een lagere sociaal -economische status (SES) en meer

comorbiditeiten. Ook blijken DM- patiënten vaker adjuvante radiotherapie te ontvangen. Er is geen verschil gevonden tussen de twee groepen wat betreft periode van diagnose, gradering van het EEC en het al dan niet roken. Verder blijkt EEC geen statistisch significant effect te hebben op DM- karakteristieken. Er zijn geen veranderingen gevonden in Hba1c en in medicatiegebruik voor en na de diagnose. Het aantal recidieven blijkt in beide groepen gelijk, namelijk 14% (respectievelijk 26 in de DM- groep en 27 in de niet DM-groep) . In de groep patiënten met EEC en DM was 31% (82 patiënten) overleden aan het einde van de follow up. In de groep patiënten met EEC zonder DM was dit 16% (228 patiënten). De 5-jaar overall overleving voor EEC- patiënten met DM blijkt significant lager dan voor EEC- patiënten zonder DM (68% versus 84%). Ook na correctie voor leeftijd, stadium, periode van diagnose, cardiovasculaire aandoeningen en behandeling bleef dit significante effect van DM op de overall mortaliteit aanwezig (HR 1.4, 95% CI: 1.0-1.8). Daartegenover staat dat geen effect van DM kon worden waargenomen bij de 388 vrouwen die overleden aan EEC , wanneer gecorrigeerd werd voor het FIGO stadium. De EEC specifieke mortaliteit, na aanpassing voor het stadium van kanker was niet significant (HR = 1.7, 95% CI: 0.7-3.9). Bij evaluatie blijkt dat van de groep patiënten met DM 54% overleed als gevolg van comorbiditeiten, terwijl in de groep patiënten zonder DM 57% overleed als gevolg van EC; dit verschil bleek statistisch niet significant.
De conclusie is dat patiënten met EEC en diabetes een slechtere overlevingskans hebben dan EEC -patiënten zonder DM. De hogere FIGO stadia bij diagnose en de multimorbiditeit bij diabetes- patiënten met EEC, vormen hiervoor de meest waarschijnlijke verklaring. EEC patiënten met DM hebben, in vergelijking met EEC patiënten zonder DM, eenzelfde kans op een recidief , maar er is wel sprake van een hogere overall mortaliteit. Na correctie voor het stadium blijkt de ziektespecifieke mortaliteit niet verschillend voor beide groepen. Verder is aangetoond dat EEC geen invloed heeft op de glycaemische controle van DM- patiënten en evenmin op complicaties bij en behandeling van DM.

Hoofdstuk 4. Kwaliteit van leven

Het meten van vooruitgang in de strijd tegen baarmoederkanker kan niet los worden gezien van de relatie met de lange termijn effecten van de behandeling en de gezondheidgerelateerde kwaliteit van leven van vrouwen die baarmoederkanker overleven. Het aantal lang overlevenden van baarmoederkanker zal de komende jaren substantieel stijgen. De verwachting is dat die stijging 3-5% per jaar zal belopen. Data van de Profiles registratie (Patient reported Outcome Following initial Treatment and Long term Survivorship) uit de periode 1999-2007 zijn gebruikt voor twee gezondheid gerelateerde analyses: een evaluatie van de bijwerkingen van radiotherapie en lymfadenectomie en een evaluatie van de invloed van hoge body mass index (BMI) op de kwaliteit van leven van overlevenden van baarmoederkanker.

Bijwerkingen van radiotherapie en lymfadenectomie

In een grote populatiestudie wordt de gezondheidgerelateerde kwaliteit van leven beschreven na lymfadenectomie (LA) zonder adjuvante regionale behandeling versus radiotherapie (RT) in het vroege stadium van endometrium carcinoom (EEC). De hypothese daarbij was dat een LA in een vroeg stadium EEC, bij het ontbreken van lymfekliermetastasen als voordeel heeft dat geen adjuvante RT zou hoeven te worden gegeven. Verondersteld werd dat dit minder morbiditeit en een betere kwaliteit van leven zou opleveren. De gezondheidgerelateerde kwaliteit van leven (HRQL) is in deze studie geëvalueerd bij overlevenden van EEC, die standaard LA kregen zonder RT in vergelijking met patiënten die geen LA ondergingen, maar wel RT kregen vanwege de aanwezigheid van risicofactoren. Voor deze studie is gebruik gemaakt van gegevens van overlevenden met een vroeg stadium EEC, die blijkens de EKR tussen 1999 en 2007 werden gediagnosticeerd. Overlevenden vulden de vragenlijsten SF-36 en de EORTC-QLQ-EN24 in. Van de 1478 aangeschreven patiënten stuurden 742 (77%) de vragenlijst ingevuld retour. Een verschil van 10-15 punten op een schaal van 0-100 wordt klinisch van betekenis geacht. Van deze groep hadden 377 (51%) vrouwen geen LA of RT (LA-RT-) gekregen; 198 (27%) vrouwen ondergingen een LA en kregen geen RT(LA + RT-); 153 (21%) vrouwen ondergingen geen LA en kregen wel RT (LA-RT+) en 14 patiënten (2%) kregen beide vormen van behandeling (LA+RT+). Vrouwen met een LA+ rapporteerden hogere scores ten aanzien van lymfoedeem symptomen (25 versus 20 punten, p = 0,04). Vrouwen die behandeld werden met RT+ scoorden hoger met betrekking tot gastro-intestinale symptomen ten opzichte van vrouwen die niet werden bestraald (RT-) (23 versus 16 punten, p = 0,04). De HRQL was vergelijkbaar tussen de vier groepen vrouwen. Dit betekent dat beide groepen vrouwen last hadden van de bijwerkingen van hun therapie. De conclusie uit bovenstaande studie is dat LA ten opzichte van adjuvante RT niet tot een verbeterde kwaliteit van leven leidt. Derhalve kan een LA niet worden aanbevolen bij vrouwen met een vroeg stadium EEC .

Invloed van de Body Mass Index (BMI) op gezondheidgerelateerde kwaliteit van leven bij overlevenden van endometriumcarcinoom

De invloed van de BMI en andere comorbiditeiten op kwaliteit van leven, met name de vermoeidheid bij overlevenden van EEC stadium I en II, wordt beschreven in hoofdstuk 4. 2. Dit betreft een dwarsdoorsnede populatieonderzoek onder EC overlevenden, gediagnosticeerd tussen 1999 en 2007 op basis van data verkregen uit de EKR. De gezondheidgerelateerde kwaliteit van leven (Health related Quality of Life (HRQoL) is gemeten met diverse vragenlijsten, waaronder de SF-36 , de EC specifieke kwaliteit van leven vragenlijst (EORTC-QLQ-EN24) en de vermoeidheid (FAS) vragenlijst . Deze vragenlijsten zijn ingevuld door 742 EC overlevenden (77%) . Van alle overlevenden met EC, hadden 478 (64%) vrouwen overgewicht (BMI≥25). De BMI bleek geassocieerd met fysieke functionaliteit (p< 0.0001), vitaliteit (p< 0.05), seksuele/vaginale problemen (p<0.0001), verandering in smaak

(p<005) en vermoeidheid (p<0.05). De BMI liet een significante stijging zien in verklarende variatie in de domeinen van fysieke functie (p<0.0001), fysieke rol (p<0.05), lichaamspijn (p<0.01), vitaliteit (p<0.01) en emotionele rol (p<0.05). Ook veroorzaakte de BMI een toename in de verklarende variatie bij EC specifieke problemen, zoals lymfoedeem (p<0.0001), seksuele/vaginale problemen (p<0.01), rug en bekken pijn (p<0.05) en, opnieuw, vermoeidheid (p<0.01). De resultaten van deze studie laten zien dat de BMI een extra impact heeft op vermoeidheid en andere domeinen van gezondheidgerelateerde kwaliteit van leven bij overlevenden van EC. Deze bevindingen zijn onafhankelijk van de andere comorbiditeiten, ofschoon die tezamen een groter effect hebben op de gezondheidgerelateerde kwaliteit van leven dan de BMI alleen. Het is van belang dat aan de BMI aandacht wordt geschonken bij onderzoek naar de kwaliteit van leven van patiënten met EC, naast andere comorbiditeiten.

Hoofdstuk 5. Visie op de rol van leeftijd en co-morbiditeit bij behandelstrategie

Wanneer wij de blik richten op de groep vrouwen met een slecht gedifferentieerd (graad 3) type EC , een hoger stadium EC, FIGO III en IV, of het EC met een ongunstig histologisch type zoals NEEC (samen ongeveer 400 vrouwen per jaar) moet geconstateerd worden dat er maar weinig vooruitgang in de vijfjaarsoverleving is te zien. Deze ongunstige tumor karakteristieken komen meer voor bij oudere vrouwen. De vijfjaarsoverleving van een graad 3 EC bedraagt 58 %; van FIGO III en IV EC respectievelijk 55% en 21% en van NEEC 54%, waaronder sereus adenocarcinoom 51% en carcinosarcoom 37%. Vrouwen met sarcomen van de uterus, 3,5% (60 vrouwen per jaar), laten wij hier buiten beschouwing. Het centraal bureau voor de statistiek (CBS) registreert de sterfte van alle uterus maligniteiten tezamen en daaruit blijkt dat de laatste decennia de mortaliteit niet daalt; ieder jaar sterven ruim 400 vrouwen aan een uterus maligniteit.

De vraag is hoe de overleving van de groep vrouwen met graad 3 EC, gevorderde stadia EC en NEEC kan worden verbeterd en de mortaliteit aan corpus uteri maligniteiten kan worden teruggedrongen. De oplossingrichtingen moeten vooral worden gezocht in verandering van de behandelstrategie. Het aantal publicaties over dit onderwerp stijgt ieder jaar. Dit is veelbelovend , maar tot heden zijn de meeste strategieën nog onderwerp van studie. Dat geldt bijvoorbeeld voor de rol van pelviene en para-aortale lymfadenectomie. Cytoreductieve chirurgie lijkt bij gevorderde stadia de overleving te verbeteren, maar dit is in gerandomiseerde studies niet aangetoond. Meerdere publicaties tonen een effect aan op de overleving van EC door adjuvante chemotherapie, vaak een combinatie behandeling met carboplatine en paclitaxel (taxol). Dit effect zou met name worden gezien bij gevorderde stadia EC en bij NEEC, maar de aantallen in deze studies zijn klein en betreffen vaak een heterogene groep patiënten. Resultaten van klinische trials, zoals nu worden ontworpen door de EORTC en de Gynecologic cancer intergroup (GCIG), moeten worden afgewacht om verdere conclusies te kunnen trekken. Of het minder vaak inzetten van uitgebreide chirurgie en/of chemotherapie invloed heeft op de overleving is niet

bekend, omdat de effectiviteit van deze behandelstrategieën niet vaststaat en onderwerp vormt van klinische trials. Maar voor het verbeteren van de overleving bij het ongunstige type EEC, dat bij oudere vouwen meer voorkomt, is meer informatie nodig. Nu worden oudere vrouwen op basis van hun comorbiditeit vaak geëxcludeerd bij klinische trials, waardoor in de klinische praktijk informatie ontbreekt hoe te handelen. Het antwoord op de vraag of bij het ongunstige endometriumcarcinoom de overleving kan worden verbeterd en de mortaliteit kan dalen, blijkt vooral te worden bepaald door karakteristieken van de patiënt. De ongunstige tumor karakteristieken graad 3 EC, gevorderde stadia EC en NEEC treden vaak op bij vrouwen ouder dan 75 jaar met een hoge prevalentie van kwetsbaarheid en multimorbiditeit en daardoor een lagere vijfjaarsoverleving en hogere mortaliteit. Het streven naar verbetering van overleving dient enigszins te worden gerelativeerd bij deze groep patiënten, omdat de prioriteit voor deze vrouwen vanwege factoren als belasting van behandeling en herstelperiode, impact op zelfredzaamheid en levensperspectief, niet ligt bij een lange overleving maar bij symptoomcontrole. Oudere patiënten die volgens een geriatric assessment fit en vitaal zijn, blijken uitgebreide chirurgie goed aan te kunnen, bij voorkeur met minimaal invasieve technieken, evenals adjuvante behandelingen met radiotherapie en chemotherapie. Het is wenselijk dat deze vitale oudere patiënten meer dan tot dusverre in klinische trials worden betrokken, zodat evidence based kan worden gekozen voor een zinvolle behandelstrategie.

EORTC vragenlijst

De 13 domeinen van de EORTC vragenlijst met endometrium kanker module en de 8 domeinen van de verkorte gezondheidsvragenlijst.

Vragenlijsten	EORTC-QLQ-EN24[1]	verkorte gezondheid vragenlijst (SF-36)[2]	10 vragen over vermoeidheid (FAS)[4]
Response score	Likert type response[3]	Likert type respons	5 punten score[5]
Schaal	Schaal 0-100 hogere score: meer symptomen	Schaal 0-100 hogere score beter functioneren	Schaal van 10-50
Domeinen	lymfoedeem	Vitaliteit	Ik voel me vermoeid
	urologische problemen	Fysiek functioneren	Ik ben snel moe
	gastro-intestinale problemen	Lichaamspijn	Ik doe niet veel op een dag
	bodyimage	Algemene beleving van gezondheid	Ik heb genoeg energie voor dagelijks leven
	spier of gewrichtspijn	Fysiek rol kunnen uitoefenen	Fysiek voel ik me uitgeput
	rug en bekkenpijn	Emotioneel rol kunnen uitoefenen	Ik heb moeite op gang te komen
	seksuele en vaginale problemen	Sociaal de rol kunnen uitoefenen	Ik kan niet goed helder denken
	tintelingen/gevoel-loosheid	Mentale gesteldheid	Ik heb geen zin iets te doen
	haaruitval		Geestelijk voel ik me uitgeput
	smaak verandering		Ik kan me als ik iets aan het doen ben niet goed concentreren
Schaal	Hogere score: gunstiger voor volgende items:		
Seksualiteit	libido		
	seksuele activiteit		
	plezier in seks		

[1] Kwaliteit van leven vragenlijst door EORTC ontwikkeld met een Endometrial Cancer Module; [2] Short form-36; [3] Likert type is een 4 punt score: 1= helemaal niet 4= heel vaak; [4] FAS= Fatigue assesment scale; [5] 1=nooit, 5= altijd

Publications related to this thesis

1. Boll D, Karim-Kos HE, Verhoeven HA, Burger CW, Coebergh JW, van de Poll-Franse LV et al. Increased incidence and improved survival in endometrioid endometrial cancer diagnosed since 1989 in The Netherlands: a population based study. Eur J Obstet Gynecol Reprod Biol 2013; 166(2):209-214.
2. Boll D, Verhoeven RH, Aa van der M.A., Coebergh JW, Doorn van H.C. Incidence and survival trends of uncommon corpus uteri malignancies in the Netherlands, 1989-2008. Int J Gynecol Cancer 2012; 22:599-606
3. Boll D, Pijnenborg JM, Nout RA, Lybeert ML, Poll-Franse L, Coebergh JW et al. Reduced adjuvant radiotherapy based on increasingly evidence-based treatments of patients with endometrioid endometrial carcinoma resulting in similar survival in the Netherlands between 1994-2009. Submitted to Radiatiotherapy Oncology
4. Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer 2011; 47(10):1504-1510.
5. Zanders MM, Boll D, van Steenbergen LN, van de Poll-Franse LV, Haak HR. Effect of diabetes on endometrial cancer recurrence and survival. Maturitas 2013; 74(1):37-43.
6. van de Poll-Franse LV, Pijnenborg JM, Boll D, Vos MC, van den Berg H, Lybeert ML et al. Health related quality of life and symptoms after pelvic lymphadenectomy or radiotherapy vs. no adjuvant regional treatment in early-stage endometrial carcinoma: a large population-based study. Gynecol Oncol 2012; 127(1):153-160.
7. Oldenburg CS, Boll D, Nicolaije KA, Vos MC, Pijnenborg JM, Coebergh JW, et al. The relationship of body mass index with quality of life among endometrial cancer survivors: a study from the population-based PROFILES registry. Gynecol Oncol 2013 Apr;129(1):216-21
8. D. Boll, H. A. Maas, J.W. Coebergh, C.W. Burger, H.C. van Doorn. Debate on the applicability of survival improvement and reduction of mortality in the elderly with unfavourable types of uterine malignancies. Submitted Obstetrics and Gynecology

Other publications

a. Mol BW, Boll D, De KM, Heintz AP, Sijmons EA, Oei SG et al. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. Gynecol Oncol 2001; 80(2):162-167.
b. Boll D, Geomini PM, Brolmann HA, Sijmons EA, Heintz PM, Mol BW. The pre-operative assessment of the adnexal mass: the accuracy of clinical estimates versus clinical prediction rules. BJOG 2003; 110(5):519-523.

c. Holman FA, Martijnse IS, Traa MJ, Boll D, Nieuwenhuijzen GA, de Hingh IH, et al. Dynamic article: Vaginal and perineal reconstruction using rectus abdominis myocutaneous flap in surgery for locally advanced rectum carcinoma and locally recurrent rectum carcinoma. Dis Colon Rectum 2013 Feb;56(2):175-85.
d. Vanderbeke I, Boll D, Verguts JK. [Pregnancy and childbirth in a patient with a spinal cord lesion]. Ned Tijdschr Geneeskd 2008; 152(20):1169-1172.
e. van de Poll-Franse LV, Nicolaije KA, Vos MC, Pijnenborg JM, Boll D, Husson O et al. The impact of a cancer Survivorship Care Plan on gynecological cancer patient and health care provider reported outcomes (ROGY Care): study protocol for a pragmatic cluster randomized controlled trial. Trials 2011; 12:256.
f. Pijnenborg JM, Boll D, Hermans RH. Comment on: Recurrence rate in vulvar carcinoma in relation to pathological margin distance [Groenen SMA, Timmers PJ, Burger CW. Int J Gynecol Cancer. 2010;20:869-873]. Int J Gynecol Cancer 2011; 21(5):794.
g. Nicolaije KA, Ezendam NP, Vos MC, Boll D, Pijnenborg JM, Kruitwagen RF et al. Follow-up practice in endometrial cancer and the association with patient and hospital characteristics: a study from the population-based PROFILES registry. Gynecol Oncol 2013; 129(2):324-331.
h. Boll D, Hermans R.H , van der Putten H.M.W.M, Kruitwagen R.F.P.M, van den Eijnden-van Raaij A.J.M, van Eenbergen M.C.H.J. Nuttige diensten van regionaal EPD. Medisch Contact, 2009 64 (21) 942-945.

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Curriculum vitae

Dorry Boll was born in Oss. In 1982 she graduated from gymnasium β at Maurick college in Vught. Subsequently, she studied medicine at the University of Utrecht. After obtaining her medical degree in 1990 , she worked at the department of gynaecology and obstetrics in the Maria hospital in Tilburg. In 1992 she started her residency in gynaecology and obstetrics at the Academic Medical Centre of Utrecht (head: Prof. dr APM Heintz and Prof. dr GHA Visser) and at the Rijnstate hospital in Arnhem (head: Dr A. Huisman) . In 1998 she began her fellow ship gynaecologic oncology in the Academic hospital Utrecht (chairman: Prof dr APM Heintz, in cooperation with Dr E. Witteveen and Dr I.M. Jürgenliemk-Schulz), at the Northern Gynecologic oncology Centre in Gateshead upon Tyne (chairman: Mr J.M. Monaghan and Mr A de Barros Lopes) , Radboud University Medical Centre Nijmegen (oncologic urology chairman: Prof. dr FM Debruyne and Dr J.A.Witjes) and University Medical Centre Gasthuisberg Leuven (chairman: Prof I. Vergote and Prof F. Amant). In 2000 she became a gynaecologic oncologist and started working at the gynaecologic department of the Catharina hospital in Eindhoven. In 2004 she funded together with Dr H.W.H.M. van der Putten, Dr R.F. Kruitwagen and Dr J. de Graaff the Organisation of Oncologic Gynaecology (OOG) in the comprehensive cancer south region (IKZ). She developed with Dr R.F. Kruitwagen and Dr L. Van de Poll-Franse and Drs S.A. ter Haar- Eck the web-based registration program Rogy. From 2006-2009 she participated in the department of gynaecology and obstetrics at the VieCuri Medical Centre next to her work as gynaecologic oncologist in OOG-IKZ. In august 2009 she moved from location Catharina hospital Eindhoven of OOG-IKZ to location in TweeSteden Hospital and St Elisabeth hospital in Tilburg (nowadays Elisabeth-TweeSteden hospital) , to succeed Dr R.F. Kruitwagen, where she now enjoys to work with het gynaecologic oncology colleagues J.M. A. Pijnenborg and J.M.J. Piek. Dorry also enjoys to work as consultant for gynaecologic oncology in Jeroen Bosch Hospital in Den Bosch, where she actively participates in the complex surgery for endometrial cancer and ovarian cancer patients.

She actively participates in the tumour committee of the comprehensive cancer South, the GeriOnNe foundation and the Dutch Gynecolgic Oncology Group. In January 2014 she will become chairwoman of the Dutch Committee on Gynecologic oncology guidelines.

Erasmus University Rotterdam
PHD PORTFOLIO
Summary of PhD training and teaching
PHD Portfolio
Name PhD : D. Boll
Erasmus department: Gynecologic oncology and Public Health
Period: 1-7-2009 t/m 1-7-2013
Promotores : Prof. dr J.W.W. Coebergh/ Prof. dr C.W. burger
Co-promotor: Dr H.C. van Doorn

1. PhD related courses, seminars and workshops

Courses seminars and workshops (registered in GAIA)	Year	workload	ECTS
General course obstetrics & gynaecology	2009	8	0,2
Committee gynaecologic oncology guidelines	2009	8	0,2
General course obstetrics & gynaecology	2009	4	0,1
General course obstetrics & gynaecology	2009	12	0,3
General course obstetrics & gynaecology	2009	12	0,3
Committee gynaecologic oncology guidelines	2009	8	0,2
General course obstetrics & gynaecology	2010	4	0,1
General course obstetrics & gynaecology	2010	4	0,1
General course obstetrics & gynaecology	2010	4	0,1
General course obstetrics & gynaecology	2010	12	0,3
General course obstetrics & gynaecology	2010	12	0,3
General course obstetrics & gynaecology	2010	12	0,3
Committee gynaecologic oncology guidelines	2010	4	0,1
Gerionne elderly and cancer	2011	4	0,1
General course obstetrics & gynaecology	2011	12	0,3
General course obstetrics & gynaecology	2011	2	0,1
General course obstetrics & gynaecology	2011	4	0,1
General course obstetrics & gynaecology	2011	3	0,1
General course obstetrics & gynaecology	2011	4	0,1
General course obstetrics & gynaecology	2011	4	0,1
General course obstetrics & gynaecology	2012	4	0,1
General course obstetrics & gynaecology	2012	12	0,3
General course obstetrics & gynaecology	2012	12	0,3
General course obstetrics & gynaecology	2012	4	0,1

General course obstetrics & gynaecology	2012	4	0,1
General course obstetrics & gynaecology	2013	4	0,1
General course obstetrics & gynaecology	2013	14	0,3
General course obstetrics & gynaecology	2013	4	0,1
General course obstetrics & gynaecology	2013	4	0,1
Meeting with promotores	2009	24	0.6
Meeting with promotores	2010	24	0,6
Meeting with promotores	2011	24	0,6
Meeting with promotores	2012	24	0,6
Meeting with promotores	2013	24	0,6

Presentations

Population based study on endometrium carcinoma in the region of the Dutch Comprehensive region South 1995-2006.	2009	4	0,3
40 jaar Nederlandse zorg endometrium carcinoom: progress against Cancer, landelijk KWF project	2010	4	0,3
HPV en cervix carcinoom en HPV vaccinatie	2010	4	0,3
overzicht endometrium carcinoom stadium I in IKZ regio 1995-2008	2011	4	0,3
ROGY webbased data	2010	4	0,3
Gerionne ouderen en kanker	2011	12	0,3
Poster: adherence to national guidelines	2012	12	0,3
Rogy symposium	2013	4	0,1
Can we improve survival and mortality in the unfavourable type of endometrial carcinoma?, gynaecongres may 2013	2013	4	0,1

International conferences

ESGO	2009	28	0,7
IGSC	2010	32	0,8
ESGO	2011	28	0,7
		431	11,2

2. Teaching and other

Other

Member of guideline commitee for gynecologic oncology	2012	24	0,6
Full time gynecologic oncologist in the Netherlands	since 2000	1000/yr	100

Teaching			
participaring in eductation of residents gynecolgy and obstetricss	since 2000	100/yr	10
participaring in eductation of interns	since 2000	30/yr	3
Supervising residents and fellows in operation theatre	since 2000	320/yr	30
Total		5923	155,5

Stellingen

behorend bij het proefschrift

Corpus Uteri Malignancies in The Netherlands since the 1980's

Registry-based studies of variation in incidence and outcome

1. In de periode 1989-2009 is sprake van een significante stijging van het endometrioide endometriumcarcinoom (EEC), met name FIGO (1988) stadium IB, graad 1 en 2. (dit proefschrift)

2. De incidentie van het carcinosarcoom is in de periode 1989-2008 niet significant toegenomen, zulks in tegenstelling tot de verwachting gebaseerd op de stijging van tamoxifengebruik bij borstkanker. (dit proefschrift)

3. In de periode 1994-2009 blijkt sprake van een afname van overbehandeling bij patiënten met stadium I EEC; de significante afname van adjuvante radiotherapie heeft geen invloed gehad op de overleving. (dit proefschrift)

4. Hoewel patiënten met EEC en diabetes een slechtere overleving hebben dan patiënten zonder diabetes, blijkt de ziektespecifieke mortaliteit na correctie voor stadium niet te verschillen. (dit proefschrift)

5. Een hoge BMI heeft onafhankelijk van andere co-morbiditeiten een aantoonbare invloed op vermoeidheid en gezondheidsgerelateerde kwaliteit van leven bij overlevenden van EEC. (dit proefschrift)

6. Ondanks de algemene verbetering van overleving bij mensen met kanker, blijft die bij oudere patiënten achter, met name bij vrouwen. (Quaglia A , EUROCARE Eur J Cancer 2009)

7. De meerderheid van overlevenden van endometrium carcinoom is obese en loopt als gevolg daarvan een groter risico op voortijdig overlijden. Verandering van levensstijl in de vorm van meer bewegen en reduceren van gewicht is belangrijk. (Von Gruenigen V , Gynecol Oncol 2012)

8. De belangrijkste oorzaak van bias bij de relatieve survival- en mortaliteitsratio hangt samen met een gebrek aan vergelijkbaarheid van de groep met kanker en de controlegroep zonder kanker. (Sarfati D et al. Int J Epidemiol. 2010)

Stellingen

9. Conditionele relatieve overleving na de diagnose kanker is een betere maat om de verbetering van behandeling van kanker te meten dan de relatieve overleving vanaf het tijdstip van diagnose. (Shack Cancer Epidem. 2013)

10. Gezien de verregaande implicaties, waaronder ook juridische, van invoering van kwaliteitsindicatoren en methodes om kwaliteit te meten, moet de ontwikkeling en implementatie daarvan plaatsvinden op basis van een hoog niveau van wetenschappelijk bewijs en een hoge mate van objectiviteit. (Das A et al Int J Radiat Oncol Biol Phys 2012)

11. 's-Hertogenbosch dankt haar trotse bezit van de kathedrale basiliek van St. Jan onder meer aan de omstandigheid, dat tijdens de anderhalve eeuw durende bouw nog geen inspraak- en planologische procedures van toepassing waren zoals thans gebruikelijk.

Dorry Boll
20 december 2013