A step-by-step approach to early stage cervical cancer treatment

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1

General introduction

General introduction

Although there is a steady decline in the incidence of cervical cancer in Western countries, and a vaccination programme against cervical cancer related HPV subtypes has recently been issued in many countries, the disease remains one of the most frequent malignancies in women, especially in developing countries. In Western countries, early stage cervical cancer has a relatively good prognosis, but often to the expense of severe morbidity. As almost half of patients are of younger age and childbearing capacity is at stake, there is a need for a therapeutic approach that retains the achieved oncological results but reduces morbidity.

1. Epidemiology of cervical cancer

The incidence of cervical cancer is 6.9 /100.000 women/year in Western Europe, but is as high as 34.5/100.000 women/year in Eastern Africa. The mortality rate is 2.0 and 25.3/100.000 women/year in Western Europe and in Eastern Africa, respectively [1, 2]. The striking difference in incidence and mortality is mainly due to the use of screening programmes in developed countries, although socioeconomic factors also play a role, as already a small decline in incidence was seen in European countries before the use of screening programmes [3].

The main risk factor for cervical cancer is infection with an oncogenic Human Papilloma Virus (HPV) [4]. A further decline in incidence is to be expected in most European countries as a result of vaccination programmes against HPV types 16 and 18. However, these two HPV types are responsible for only 70% of all cervical cancers, with other HPV subtypes associated to a variable extent according to geographical regions [5, 6, 7]. Furthermore, the full effect of vaccination will only be seen decades from today and will be largely dependent on compliance to the programme [8, 9]. An additional risk factor is the failure to comply with the PAP smear screening programme for cervical cancer, which in The Netherlands has a mean compliance of only 60-70%, ranging from highest to lowest compliance in urban and in rural areas, respectively [10]. In the Netherlands, the peak incidence of cervical cancer lies between 40 and 45 years of age. More than 40% of women with stage I disease will be under 40 years of age at diagnosis [11]. As the average age of primiparity in the Netherlands is 29.4 years [12], prevention and early detection not only play a role in survival, but also could have an effect on preservation of fertility in women at risk of cervical cancer.

2. Diagnosis and staging

2.1 Histology

The most common cervical cancer type is squamous cell carcinoma (85%), followed by adenocarcinoma (15%). Diagnosis of cervical cancer is done by pathology, obtained through biopsy of the cervix, through large loop excision of the transformation zone (LLETZ) or through conisation.

2.2 International Federation of Gynaecology and Obstetrics (FIGO) staging system.

Staging will define the extent of disease and is, consequently, paramount for the choice of therapy. FIGO staging is mainly based on the results of physical vaginal examination (if necessary carried out under anaesthesia), and histopathology of material obtained by cervical biopsy (or conisation) and/or endocervical curettage [13, 14]. Colposcopy, radiography, and endoscopy are also allowed for FIGO staging, but the latter two techniques are mostly informative only for advanced stages, and are mainly used to *exclude* them. The accessibility of FIGO staging procedures in developing, as well as developed countries, allows for homogeneous staging throughout the world and, consequently, for comparision of incidence, efficacy of treatment and survival of cervical cancer.

Although officially cervical cancer is staged clinically according to the directives of the FIGO, at present there are more techniques available for accurate staging of the disease than those allowed within the FIGO staging system. Information can be gained on several prognostic factors, such as lymph node involvement, tumor size, lymphovascular space invasion (LVSI), and serum tumor markers, which can be used to adjust treatment options and prognosis [15]. A major prognostic factor in cervical cancer, lymph node status, is not considered in FIGO staging, as this staging system is also used in countries without access to imaging techniques able to evaluate it [15, 16, 17, 18].

Beyond cervical biopsy and pelvic examination, the allowed FIGO staging procedures are usually uninformative for patients with stage IA1 to IB2 cervical cancer, which constitute the majority of patients diagnosed in developed countries [19]. The limitations of FIGO staging, especially in stage IB tumors where the only observable difference is the size of the tumor, is closely related to its incapacity to define the status of the lymph nodes. Survival is more closely related with lymph node status than with tumor size: large tumors with negative lymph nodes have a better outcome of disease than small tumors with positive lymph nodes [20]. On the other hand, large tumors, designated as bulky disease, are more often associated with positive lymph nodes than small tumors. The 5-year survival rate for stage IBI cervical cancer is 87-92% [21] without lymph node metastases, but falls to 57% when metastases are present. [Fig. 1]

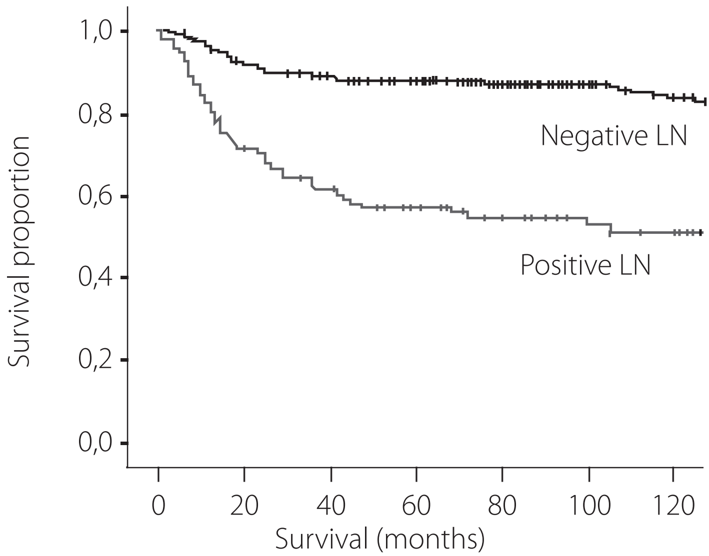

Figure 1. Kaplan-Meier analysis, showing disease free survival, of FIGO stage IB-IIA cervical cancer according to lymph node involvement ($p < 0.01$). Modified from Sartori et al. [15]. Survival of stage IB-IIA cervical cancer is directly related to lymph node metastasis.

2.3 Imaging techniques to define extent of disease

Non-invasive techniques to define extent of disease are continually evolving because of the importance of it in the choice of treatment. Imaging techniques can facilitate the detection of lymph node or distant metastases, as well as the extent of local disease, such as the presence of parametrial invasion.

Computed tomography (CT) makes use of x-ray images and is primarily used to evaluate the size of the cervix and to detect enlarged lymph nodes, obstruction of the ureter, metastases or parametrial involvement. However, the information provided is subject to the size of the lesions, as demonstrated by Bipat e.a. in a systematic review evaluating both CT and MRI [22].

Magnetic resonance imaging (MRI) makes use of radiofrequency pulses, and gives a superior soft tissue contrast resolution than does CT. Additionally to the information provided by CT, MRI is better suited to determine parametrial invasion (sensitivity 74% compared to 55% for CT), and bladder and rectal invasion (sensitivity 75% vs 71%, respectively). Nevertheless both fail in identifying small (< 1 cm) lymph node metastases, which is a crucial limitation (sensitivity for lymph node metastases 60%

vs 43%, respectively) [22, 23]. In order to enhance sensitivity several more advanced techniques for MRI can be used such as dynamic contrast-enhanced MRI (DCE-MRI), diffusion weighted MRI (DWI-MRI) or MR spectroscopy (MRS).

DCE MRI uses sequential images and in addition gadolinium based contrast agents, and is mainly used to measure tumor size as response to therapy [24]. DWI-MRI is sensitive to the microscopic motion of water molecules, and uses water diffusion properties to characterise tissues as being tumor-positive. DWI-MRI is capable of predicting lymph node metastases, with a sensitivity of 83%, but seems less suited to detect lymph node metastases in lymph nodes smaller than [25, 26, 27, 28]. Current studies on its use reflect the role of DWI-MRI in assessing cervical tumor response to nonsurgical therapy [29, 30]. MR spectroscopy measures the levels of metabolites in tissues, differentiating between benign and malignant tissue. The clinical use, however, is limited due to artefacts in vivo caused by paracervical fat and bowel movements [31].

Radio- labelled 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) detects the metabolic activity of tissues by their uptake of radio labelled 18-fluorodeoxyglucose (FDG). Mainly proliferating and inflammatory cells have a high FDG uptake. FDG-PET can detect lymph node metastases with high sensitivity and specificity. In cervical cancer there is a high correlation between FDG-PET lymph node findings and patient survival. In early stage cervical cancer however, its role may be limited as demonstrated by Chou e.a., who found that only one out of ten lymph node metastases (10%) was detected by FDG-PET. This was probably due to the relatively low percentage of lymph node positive patients (16.7%) and to the size of tumor inside positive lymph nodes (median lymph node size, 15 x 7 mm, and median tumor component size, 4.0 x 3.0 mm) [32]. Another limitation of FDG-PET is the lack of information on an exact anatomic location of the detected lesion [33].

To overcome the limitations of radiographic imaging and improve the detection of lymph node metastasis, PET and CT images are combined: PET/CT provides the detailed structural information of CT combined with the metabolic activity of the affected lymph nodes. This significantly increases the accuracy of the detection of lymph node metastases compared to CT and MRI [34]. PET/CT is valuable for preoperative lymph node staging, and can also be used as an indicator of response to treatment and prognosis in cervical cancer [35]. However, because of the failure in identifying small tumour masses, it does not exclude the necessity of performing surgical staging of the lymph nodes especially in early stage disease [36, 37].

2.4 Surgical staging

With the introduction of minimal invasive techniques, such as laparoscopy, it became possible to perform a minimally invasive assessment of nodal status, even as a separate laparoscopic procedure independently of a radical hysterectomy [38, 39]. Laparoscopy is a proven safe and minimal invasive part of the treatment of early stage cervical cancer that is used worldwide to date to assess lymph node status [40]. When combined with a sentinel lymph node (SLN) procedure and the use of immunohistochemistry (IHC) to evaluate the SLN, an accurate assessment of nodal status and occult metastases can be made, providing the option of tailored treatment for early stage cervical cancer, with emphasis on minimal invasive techniques [41,42,43,44].

Conceptually, SLN are defined as the first lymph nodes draining the lymph flow from an organ, and, in case of malignant disease, they will be the first to be affected by lymphatic dissemination of the tumor. Histologically tumor-negative SLN predict that also the remaining lymph nodes will be negative [45]. The laparoscopic SLN procedure is based on the detection and assessment of these specific lymph nodes. It has the potential benefit of decreasing nerve, blood and lymph vessel and ureteral injuries, reducing blood loss and generally reducing the morbidity compared to normal lymphadenectomy. The SLN procedure is currently standard treatment in breast cancer, malignant melanoma, and vulvar cancer. A few ongoing studies address the issue of the possibility of omitting full lymphadenectomy in case of a negative SLN in cervical cancer [46].

3. Treatment

Treatment of early stage cervical cancer consists of surgery when possible, radiotherapy when needed, or a combination of surgery and radiotherapy, or neoadjuvant chemotherapy and surgery.

3.1 Surgery

For early stage (IA2-IIA) cervical cancer standard surgery consists of radical hysterectomy with pelvic lymphadenectomy. The basis of this surgery dates back to the early twentieth century, when Ernst Wertheim described his first 500(!) cases in "Die erweiterte abdominale Operation bei Carcinoma Colli Uteri" [47]. Wertheim's operation consists of the removal of the uterus including the cervix, parametria and, if nodal involvement was obvious, pelvic nodes up to the aorta. The abdominal route of Wertheim's operation represented an improvement (but with a higher mortality rate) on the vaginal route as performed by Schauta, as it was technically superior to resect lymph nodes through the abdominal route [48]. The Wertheim operation was popular until the early 1920s, when radiotherapy was introduced and proved to be a good and less dangerous alternative to surgery. Joe-Vincent Meigs, however, stressed the need of systematic lymph node dissection, which he re-introduced after the second-world war when the operative risks were much lower than in Wertheim's time. Because of specific drawbacks of radiotherapy (radiation resistance, recurrences in previously irradiated patients), radical hysterectomy became popular again in a modified form known as the Wertheim-Meigs operation, mainly introducing a full lymph node dissection in all cases and not only in patients with gross nodal involvement [49]. The discovery of antibiotics, the use of blood replacement therapy and more advanced techniques contributed towards a perioperative mortality rate of almost 0%. Other modifications, such as that of Okabayashi, introduced a more radical dissection of the parametrium and sacrouterine ligament, but the basic surgical procedure remained the same [50].

In the second half of the twentieth century, the role of lymph node metastases became increasingly clear as an independent prognostic factor. Finally, its occurrence would become one of the main indications for adjuvant therapy [51].

With the introduction of laparoscopy as a tool for minimal invasive surgery in the late 1980's promoted by pioneers like Dargent, Childers and Nezhat [38, 52, 53] it has become possible to perform not only a lymphadenectomy in early stage cervical cancer, but also a radical hysterectomy with full lymphadenectomy by laparoscopy [54]. Today, this operation is often performed by means of robot assisted laparoscopic surgery, such as the da Vinci® Surgical System (dVSS, Intuitive Surgical, Mountain view CA). The method is being subjected to trials to compare the classic open radical hysterectomy or laparoscopic radical hysterectomy with the endoscopic (robot assisted) route [54, 55]

New concepts for minimal invasive surgery have risen since the mid-eighties for small (under 2 cm diameter) stage IA2-IB1 cervical carcinomas, and when childbearing is at stake, culminating in the radical vaginal trachelectomy (RVT) combined with pelvic lymph node dissection (PLND), as described by Dargent [56]. With this technique, it is possible to retain the uterus and fertility can be preserved. Up to date, over 1000 cases worldwide have been described, with a 40% birth rate (healthy newborn at term). Alternatively, the trachelectomy can be performed abdominally by laparotomy (abdominal radical trachelectomy, ART) or by laparoscopy. Both techniques are used today and differential indications are being evaluated [57, 58].

Alternatively, a LPLND may be combined with a conisation, sometimes preceded by neo-adjuvant chemotherapy as advocated by Landoni [59, 60]. This approach is not used as standard treatment to date and is considered experimental therapy in need of further evaluation [58].

A great advantage of minimal invasive surgical staging (laparoscopic lymphadenectomy) is, apart from less invasive surgery the avoidance of radical hysterectomy and thus of its added morbidity in patients with positive lymph nodes, who will need chemoradiation as primary treatment [61].

3.2 Radiotherapy and chemotherapy

Radiotherapy as treatment compared to surgery alone shows an equal effectiveness in terms of survival as demonstrated by Landoni e.a. in the only randomized study comparing 343 stage IB/IIA cervical cancer patients with an overall survival of 80% vs. 82%, respectively [62]. When the uterus is in situ, external-beam radiation is combined with intracavitary brachytherapy. A trial conducted by the Radiation Therapy Oncology Group (RTOG) showed that 5-year survival rates increased from 58 to 73% in case of early stage (bulky) cervical cancer with the addition of chemotherapy (cisplatin) to radiation therapy compared to radiation therapy only. There was also a significant increase in disease –free survival and reduction of local recurrences and distant metastases. [63]. Together with two further studies the findings led to the 1999 National Cancer Institute (USA) alert, dictating chemoradiation for all cases needing adjuvant treatment [64, 65, 66].

Despite these findings, surgery remains the treatment of choice for early stage cervical cancer as morbity due to radiation damage such as vaginal stenosis, loss of fertility, sexual dysfunction, atrophy of sexual organs and radiation enteritis remain major drawbacks of radiotherapy [67].

To date, in western European countries primary (chemo-) radiation in early stage cervical cancer is mostly reserved for bulky disease and for cases where tumor-positive lymph nodes or locally advanced disease is found at surgery.

3.3 Neoadjuvant chemotherapy

Chemotherapy reduces tumor size and treats lymph node and systemic disease [68]. Although Sardi e.a. found a significant increase in disease-free survival in early stage cervical cancer when chemotherapy was administered prior to surgery, this was only the case for bulky disease [69]. As such, neoadjuvant chemotherapy is mainly used in early stage cervical cancer prior to surgery when reduction of tumor load is necessary [70]. At present, a phase III trial by the European Organization for Research and Treatment of Cancer (EORTC), comparing neoadjuvant chemotherapy

Table 1. Current treatment modalities for early stage cervical cancer and their advantages and disadvantages / morbidity.

Treatment	Advantages	Disadvantages / morbidity
Surgery		
Radical hysterectomy	- preservation of ovarian function - accurate assessment of pathologic extent of disease - short overall treatment time	- depends on radicality of surgery - loss of fertility - sexual dysfunction (mainly depending on radicality of surgery) - nerve damage - bladder dysfunction - ureterovaginal or vesicovaginal fistulas
Laparoscopic (conventional or robot assisted)	- comparable to radical hysterectomy but less morbidity, shorter hospital stay	- Less nerve damage - shorter hospital stay - (long) learning curve and expensive equipment (robot) needed - Not yet standard treatment
RVT or ART	- preservation of fertility - less morbidity than RH	- not yet standard treatment - learning curve - only for small stage (tumors < 2 cm diam) - sometimes necessitating neoadjuvant chemotherapy
Conisation (combined with (laparoscopic) lymphadenectomy)	- very little morbidity - short hospital stay - preservation of fertility	- As to date only in research setting - for very small stage cervical cancer only?
Radiotherapy	- feasible and effective in almost all patients - good pelvic control	Acute - diarrhoea - abdominal cramps - nausea Long term - loss of fertility - radiation damage to surrounding structures, leading to long-term enteritis and cystitis - vaginal stenosis or necrosis - sexual dysfunction - atrophy of reproductive organs
Chemotherapy	- good distant control - radio-sensitizer when administered concurrent with radiotherapy	- loss of ovarian function - nausea, vomiting - (chronic) fatigue - alopecia - nephrotoxicity - hypersensitivity - anemia

and surgery to chemoradiotherapy in early stage bulky disease and higher stages is ongoing [71]. For stage IB1 cervical cancers neoadjuvant chemotherapy is used in trials to reduce tumor volume prior to minimal invasive surgery, such as a conisation or radical vaginal trachelectomy [72].

4. Objectives of this thesis

This thesis investigates methods to predict tumor status and prognosis as an aid towards establishing patient tailored treatment.

4.1 ***Part I****: Are tumor markers predictive for occult disease in early stage cervical cancer?*

The **first** study of this thesis (chapter 2) analyses the prognostic role of tumor markers. We investigated whether pre-treatment analysis of a combination of tumor markers (SCC-Ag, CYFRA 21-1, CA 15-3 and CA 125) could identify high-risk patients with early stage cervical cancer. Our hypothesis was that a combination of elevated tumor markers would identify a subgroup of patients with a higher chance of occult disease and a poorer prognosis, which would be best served with chemoradiation therapy. This could be a first step to exclude high- risk patients from a surgical approach, and thus minimize the risk of additional morbidity in case of a radical hysterectomy followed by (chemo-) radiation therapy.

The **second** study (chapter 3) analysed the combination of pre-treatment SCC-Ag levels and lymph node status in relation to disease outcome in early stage cervical cancer. The aim of this study was to establish a cut-off level of SCC-Ag able to identify patients at risk for occult disease in the absence of positive lymph nodes.

4.2 ***Part II****: Can sentinel lymph node detection, laparoscopy and radical vaginal trachelectomy tailor surgical treatment in early stage cervical cancer?*

The **third** study (chapter 4) consisted of a systematic review of the diagnostic performance of SLN detection for minimal invasive assessment of nodal status (in terms of metastases) in early stage cervical cancer, and to determine which technique (blue dye, Technetium-99m colloid or the combined method) had the highest success rate in terms of detection rate and sensitivity. A high sensitivity and specificity of the SLN procedure would contribute towards identifying patients eligible for minimal invasive surgery on the one hand, or best treated by chemo radiation on the other.

The **fourth** study (chapter 5) evaluated retrospectively the safety of a laparoscopic approach in cervical cancer patients, in particular of lymphadenectomy. Patients who underwent an abdominal radical hysterectomy and open lymphadenectomy were compared with patients who underwent a laparoscopic lymphadenectomy, followed by abdominal radical hysterectomy if indicated. Outcome measures were safety of the procedure, pattern of recurrence and survival. Aim was to prove that the use of laparoscopy for lymphadenectomy has no detrimental effect on outcome in terms of overall and disease specific survival, and thus can be safely applied to early stage cervical cancer.

In the **fifth** study (chapter 6) we analysed the oncologic and obstetric outcome of radical vaginal trachelectomy for the first 67 cases performed in the Netherlands to illustrate the feasibility of the implementation of minimal invasive surgery in early stage cervical cancer.

With the combination of these studies we endeavoured to take the treatment of early stage cervical cancer a step further towards individualized treatment that minimizes morbidity and, whenever possible, retains fertility without jeopardizing the good results that have been achieved with conventional approaches.

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2

A combination of serum tumour markers identifies high risk patients with early stage squamous cervical cancer.

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Abstract

We aimed to investigate whether pretreatment serum levels of squamous cell carcinoma (SCC) antigen (SCC-Ag), cytokeratin 19 (CYFRA21-1), and two mucins (CA15-3 and CA125) identify patients with occult disease in early-stage SCC of the cervix. Therefore, pretreatment serum samples were obtained from 78 patients with SCC of the cervix (52 IB, 9 IIA and 18 IIB), and tumour markers were measured with commercial immunoassays. SCC-Ag, CYFRA 21-1 and CA15-3 (analysed as continuous variables) were significantly associated with overall (OS) and disease-free survival (DFS) in univariate analysis ($p<0.001$ in all cases). Multivariate analysis identified lymph node status as the strongest predictor for OS and DFS ($p<0.001$ and $p = 0.001$, respectively), followed by CYFRA 21-1 ($p = 0.060$ and $p = 0.027$, respectively), and CA15-3 ($p = 0.082$ and $p = 0.017$, respectively). Clinical cut-off values for each marker were defined by maximizing the log-rank statistic for overall survival (OS) in the total population as 1.1 µg/L for SCC-Ag (N 47, 60.3%), 1.4 µg/L for CYFRA 21-1 (N 47, 60.3%), 40 U/mL for CA15-3 (N 11, 14.1%), and 30 U/mL for CA125 (N 10, 12.8%). Stage IB patients with positive SCC-Ag and CYFRA21-1 had significantly lower OS (mean 8.3 years, 95% CI 5.8 – 10.7 years) and DFS (mean 7.3 years, 95% CI 4.6 – 10 years) than all other stage IB patients (OS, mean 14.5 years, 95% CI 13.5 – 15.5 years; DFS, mean 13.9 years, 95% CI 12.5 – 15.4 years). Stage IB patients with tumours<4cm or with negative lymph nodes and markers positive had significantly poorer OS and DFS compared to all other patients in the same group. Elevated levels of both CA125 and CA15-3 (3 patients) were associated with an extremely poor prognosis.

In conclusion, a combination of SCC-Ag and CYFRA 21-1 may help to identify early stage cervical cancer patients with occult disease requiring adjuvant therapy.

Introduction

In spite of improvements in cervical cancer treatment, cervical cancer incidence is the second cause of cancer-related death in women worldwide, only surpassed by breast cancer [1]. Survival rates vary from 80% for women with localized cancer to 47% for those with regional cancer, and 21% for women with metastatic disease at diagnosis [2].

Treatment of early stage cervical cancer depends largely on tumor size and status of the lymph nodes, the latter constituting a major prognostic factor strongly linked with disease outcome [3]. In developed countries, imaging techniques supplementing those for FIGO staging, e.g. computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography with fluorodeoxyglucose (FDG-PET), and even surgical staging procedures have been used to assess lymph node status and, consequently, treatment outcome [1].

Prognostic factors other than lymph node status could help to definine the treatment modality most appropriate for a particular patient, and outcome of disease could be improved by proper patient selection. Tumor characteristics such as large tumor diameter, high tumour grade, vascular invasion and deep stromal infiltration have been associated with bad prognosis, and are taken into account for risk grouping of patients with early-stage squamous cell cancer (SCC) of the cervix [3, 4]. Furthermore, a variety of serum tumor markers, primarily SCC antigen (SCC-Ag), cytokeratin 19 (CYFRA21-1) and membrane-associated mucin MUC16 (CA125), have been assiciated with tumor characteristics and outcome of disease, with varying results [for a recent review see ref. 5]. The CA 15.3 assay [6] determines serum levels of MUC1, a large, membrane-associated, heavily glycosylated mucin sharing many structural characteristics with CA125 which has hardly been studied in the context of cervical cancer [7].

The aim of this study was to investigate the utility of a panel of tumour markers (SCC-Ag, CYFRA 21-1, CA15-3 and CA 125) to identify patients with early stage cervical SCC at high risk of recurrence and death that would benefit from patient-tailored adjuvant therapy.

Patients and methods

Serum samples and study population

Serum samples were obtained before primary treatment from 78 patients (52 in FIGO stage IB, 9 in FIGO stage IIA and 18 in FIGO stage IIB) with primary histologically proven SCC of the uterine cervix treated at the Free University Medical Center of Amsterdam between 1988 and 1996. All clinical charts were reviewed and patients with a prior or concomitant history of malignancy were excluded from the study. Table 1 lists the clinicopathological characteristics of the patients and their primary treatment. Information on patient outcome was reviewed until November 2006, and was available for all patients; however, 2 patients were lost to follow up in the 1st year after treatment (in 1 of them, stage IB, SCC recurred five months after primary treatment), and another 5 patients in the 2nd year; they were treated as censored observations. The principal events analyzed were recurrence and death. Disease free survival_(DFS) was defined as the time elapsed between the start of primary treatment and the first reappearance of cervical cancer at any site, or the date of the last visit for patients with no evidence of disease_(Table 1). Overall survival (OS) was defined as the time elapsed between primary treatment and death (Table 1), or the date of the last visit for all other patients. All deaths were due to cervical cancer. The median follow up of the patients with no evidence of disease after primary treatment was 5.9 years (range 0.75 – 15.7 years).

Table 1. Clinicopathological characteristic of the patients with SCC of the cervix

			FIGO stage	
Characteristics	**Total (N = 78)**	**IB (N = 52)**	**IIA (N = 9)**	**IIB (N = 17)**
Median age, years (range)	45 (22 – 80)	41 (22 – 80)	46 (31 – 79)	59 (33 – 75)
Histological grade				
I	2	2	-	-
II	23	14	2	7
III	52	35	7	10
Unknown	1	1	-	-
Tumor diameter, cm				
< 4	47	39	1	7
≥ 4	31	13	8	10
Lymph node status				
Negative	52	38	4	10
Positive	26	14	5	7
Primary treatment				
Surgery	34	32	2	-
Surgery and radiotherapy	18	13	3	2
Radiotherapy	22	6	3	13
Chemoradiation	4	1	1	2
Recurrences, n (%)	22 (28.2)	11 (21.2)	4 (44.4)	7 (41.2)
Deaths, n (%)	19 (24.4)	9 (17.3)	3 (33.3)	7 (41.2)
Median DFS, years (range)	5.1 (0.1 – 15.7)	5.3 (0.4 – 15.3)	1.4 (0.1 – 12.9)	4.4 (0.1 – 15.7)
Median OS, range (years)	5.2 (0.4 – 15.7)	5.4 (0.4 – 15.3)	3.1 (1.3 – 12.9)	4.4 (0.6 – 15.7)

Blood samples were obtained by venous puncture, allowed to clot at room temperature, centrifuged and the serum was aliquoted and stored at -80° C until analyzed.
Procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983, and in accordance with the guidelines for research of our institute.

Serum Immunoassays
Serum tumor markers were measured in serum with the following commercial immunoassays: SCC-Ag [8] with a microparticle enzyme-immunoassay system (IMx, Abbott Diagnostics, Chicago, Ill., USA); CYFRA 21-1 [9] with the CYFRA 21-1 assay (Boehringer Mannheim, Tutzing, Germany) on an automated enzyme-immunoassay system; CA15-3 with the ACS™ BR assay (Bayer Diagnostics, Mijdrecht, The Netherlands) on the Centaur system [6]; and CA125 with the Enzymun-Test CA125 II (Boehringer Mannheim) on the fully automated Enzymun-Test system ES 300 [10]. SCC-Ag, CYFRA 21-1 and CA125 were measured in 1999, and CA 15-3 in 2002. The cutoff levels recommended by the manufacturers are 1.5 μg/L for SCC, 1.4 μg/L for CYFRA 21-1, 30 U/mL for CA15-3, and 35 U/mL for CA125. Clinical cutoff values for each marker were defined by maximizing the log-rank statistic for OS in the total population as 1.1 μg/L for SCC-Ag, 1.4 μg/L for CYFRA 21-1, 40 U/mL for CA15-3, and 30 U/mL for CA125, and applied in the present study.

Statistical methods
Statistical analysis was performed using SPSS software (Version 14.0, SPSS Inc, Chicago, Ill., USA). Results in the different patient groups were analyzed using the Mann-Whitney *U*/Wilcoxon rank sum W Test. Using Pearson's χ^2 test, the distribution of marker levels above or below the clinical cutoff was analysed in contingency tables according to clinicopathological characteristics; when the sample size was small, Fisher's exact test was employed. Univariate and multivariate analysis of OS and DFS were performed in the total population using the Cox proportional hazards regression model [11]. The model included the following clinical and pathologic features as potential predictors: age, FIGO stage (IB, IIA or IIB), lymph node involvement (negative or positive), tumor diameter (<4cm or ≥4cm), histology grade (I + II or III), and SCC-Ag, CYFRA 21-1, CA15-3, and CA125 levels entered as continuous variables. The probability of OS and DFS in relation to tumor marker levels was analyzed using the Kaplan-Meier method [12], and univariate comparisons between subgroups were made using a two-tailed log-rank test;

p values ≤ 0.05 were considered statistically significant. Cutoff levels applied in the analysis were defined by maximizing the log-rank statistic for OS in the total population (clinical cutoff).

Results

Tumor marker levels and clinicopathological characteristics

Tumor marker levels assessed in the study population are listed in Table 2. They did not differ between patients with grade I, II, or III tumors.

In stage IB, SCC-Ag levels ranked significantly higher in patients with tumors≥4cm than in patients with tumors<4cm ($p = 0.006$), and in patients with positive than in patients with negative lymph nodes ($p = 0.042$), but no significant differences were observed for the other markers. In addition, no statistically significant differences in tumor marker levels in relation to tumor diameter or lymph node status were found in stage IIA and IIB for any of the four markers.

Table 2. Serum tumor marker levels (median, range) in the study population

	n	SCC-Ag (μg/L)	CYFRA 21-1 (μg/L)	CA15-3 (U/mL)	CA125 (U/mL)
Total population	78	1.6 (0.1 – 125)	1.8 (0.6 – 33)	18 (4 – 117)	16 (1– 914)
FIGO stage					
IB	52	1.2 (0.1 – 58.9)	1.4 (0.6 – 7.7)	18 (4 – 92)	13 (1 – 112)
IIA	9	2.5 (0.3 – 44.1)	1.9 (1 – 6.8)	17 (5 – 36)	21 (7 – 33)
IIB	17	8.7 (0.4 – 125)	4.4 (1.5 – 33)	27 (11 – 117)	24 (8 – 914)
P value IB/IIB		<0.001	<0.001	0.004	0.002
Tumor diameter					
<4cm	47	1.1 (0.1 – 125)	1.4 (0.6 – 33)	18 (4 – 47)	13 (1 - 77)
≥4cm	31	2.6 (0.3 – 58.9)	2.3 (0.7 – 9.4)	19 (4 – 117)	21 (7 – 914)
P value		0.001	0.003	0.005	n.s.
Lymph node					
negative	52	1.2 (0.1 – 23.3)	1.6 (0.6 – 9.4)	18 (4 – 100)	14 (1 – 628)
positive	26	2.4 (0.3 – 125)	2.1 (0.8 – 33)	18 (4 – 117)	19.5 (4 – 914)
P value		0.047	n.s.	n.s.	n.s.

The Mann-Whitney U test was performed; no significant difference was found between IB and IIA, and IIA and IIB. NS = Nonsignificant

Tumor marker levels and prognosis

Univariate and multivariate analysis of OS and DFS

Cox regression analysis of OS and DFS in relation to disease characteristics and tumor marker levels are shown in table 3. Age, histology grade and tumor diameter were not significantly associated with OS and DFS in univariate analysis. Multivariate analysis of FIGO stage, lymph node status and tumor marker levels identified lymph node status as the strongest predictor for OS and DFS, followed by CYFRA 21-1 and CA15-3.

Table 3. Correlation between disease characteristics and tumor marker levels (analyzed as continuous variables) and outcome of disease

Factors	OS		DFS	
Univariate analysis	HR (95% CI)	*P value*	HR (95% CI)	*P value*
FIGO stage IB *vs.* IIA *vs.* IIB	1.79 (1.11 – 2.91)	0.013	1.64 (1.04 – 2.58)	0.028
Lymph node neg. *vs.* pos.	11.73 (3.86 – 35.65)	<0.001	6.62 (2.67 – 16.45)	<0.001
SCC-Ag, μg/L	1.03 (1.01 – 1.04)	<0.001	1.03 (1.02 – 1.05)	<0.001
CYFRA21-1, μg/L	1.10 (1.03 – 1.16)	<0.001	1.11 (1.04 – 1.18)	<0.001
CA15-3, U/mL	1.03 (1.01 – 1.05)	<0.001	1.03 (1.02 – 1.05)	<0.001
CA125, U/mL	1.00 (1.00 – 1.01)	0.075	1.00 (1.00 – 1.01)	0.057
Multivariate analysis	OS		DFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Lymph node neg. *vs.* Pos.	9.72 (3.10 – 30.49)	<0.001	5.31 (2.08 – 13.71)	0.001
CYFRA21-1, μg/L	1.06 (0.997 – 1.13)	0.060	1.08 (1.01 – 1.16)	0.027
CA15-3, U/mL	1.02 (0.998 – 1.03)	0.082	1.02 (1.00 – 1.04)	0.017
FIGO stage IB *vs.* IIA *vs.* IIB	1.37 (0.80 – 2.33)	0.247	1.18 (0.70 – 1.98)	0.536
CA125, U/mL	1.00 (0.998 – 1.004)	0.577	1.00 (0.96 – 1.05)	0.278
SCC-Ag, μg/L	1.00 (0.95 – 1.05)	0.990	1.00 (0.96 – 1.05)	0.839

HR = Hazard ratio

Distribution of tumor marker levels in relation to clinicopathological characteristics and outcome

The distribution of negative or positive tumor marker levels and their combination in relation to clinicopathological characteristics, recurrence of disease, and death from cervical cancer are displayed in table 4. The most significant association with clinicopathological characteristics and outcome of disease was found for SCC-Ag and CYFRA 21-1 levels above the cut-off level (N 38) against all others (N 40). SCC-Ag and CYFRA 21-1 were positive in 15 of 18 patients with either CA15-3 or CA125 above the cutoff level.

Kaplan Meier OS and DFS analyses in relation to tumor marker levels

SCC-Ag and CYFRA 21-1

Kaplan Meier analysis of SCC-Ag and CYFRA 21-1 results divided into four groups

(-/-, +/-, -/+ and +/+, respectively) showed a lower OS (46% *v* 92%, $p<0.001$) and DFS (45% *v* 85%, $p < 0.001$) for patients with a concomitant elevation of SCC-Ag and CYFRA 21-1 (markers positive) than patients in the other three groups taken as a whole (markers negative). These differences in OS and DFS remained significant after adjusting for FIGO stage combined with lymph node status ($p = 0.015$ and $p = 0.002$, respectively).

Table 4. Number of patients (%) with elevated tumor marker levels in relation to clinicopathological tumor characteristics and outcome of disease

	n	SCC-Ag >1.1μg/L	CYFRA 21-1 >1.4μg/L	SCC-Ag>1.1μg/L and CYFRA 21-1>1.4μg/L	CA15-3 >40 U/mL	CA125 >30 U/mL	CA15-3 >40U/mL or CA125>30 U/mL
Total	78	47 (60.3)	47 (60.3)	38 (48.7)	11 (14.1)	10 (12.8)	18 (23.1)
FIGO stage							
IB	52	26 (50.0)	23 (44.2)	17 (32.7)	4 (7.7)	2 (3.8)	5 (9.6)
IIA	9	6 (66.7)	7 (77.8)	6 (66.7)	0	2 (22.2)	2 (22.2)
IIB	17	15 (88.2)	17 (100.0)	15 (88.2)	7 (41.2)	6 (35.3)	11 (64.7)
P value		0.009	<0.001	<0.001	0.001	0.002	<0.001
Tumor diameter							
< 4cm	47	22 (46.8)	23 (48.9)	17 (36.2)	4 (8.5)	3 (6.4)	7 (14.9)
≥ 4cm	31	25 (80.6)	24 (77.4)	21 (67.7)	7 (22.6)	7 (22.6)	11 (35.5)
P value		0.003	0.012	0.006	NS	NS	NS
Lymph node							
negative	52	27 (51.9)	28 (53.8)	22 (42.3)	4 (7.7)	5 (9.6)	8 (15.4)
positive	26	20 (79.6)	19 (73.1)	16 (61.5)	7 (26.9)	5 (19.2)	10 (38.5)
P value		0.033	NS	NS	0.036	NS	0.043
Recurrences							
no	66	29 (43.9)	28 (42.4)	20 (33.3)	5 (7.6)	5 (7.6)	10 (15.2)
yes	22	18 (81.8)	19 (86.4)	18 (81.8)	6 (27.3)	5 (22.7)	8 (36.4)
P value		0.015	0.003	<0.001	NS	NS	NS
Deaths							
no	59	31 (52,5)	30 (50.8)	22 (37.3)	6 (10.2)	6 (10.2)	11 (18.6)
yes	19	16 (84.2)	17 (89.5)	16 (84.2)	5 (24.4)	4 (21.1)	7 (36.8)
P value		0.014	0.003	<0.001	NS	NS	NS

Pearson χ^2 test or, for small sample sizes, Fisher's exact test was applied. NS =Nonsignificant

SCC-Ag and CYFRA 21-1 in Stage IB

Results for stage IB are shown in Table 5 and Figures 1 and 2. Results were very similar in the total population (not shown).

OS was lower (44% *v* 94%, $p = 0.001$) for marker-positive patients (mean 8.27 yrs, 95% CI 5.84 - 10.71 yrs) than for marker-negative patients (mean 14.49 yrs, 95% CI 13.46 – 15.52 yrs). These differences remained significant after adjusting for tumor diameter ($p = 0.003$), and lymph node status ($p = 0.018$). DFS was also lower (44% *v* 86%, $p = 0.001$) for marker-positive (mean 7.32 yrs, 95% CI 4.64 - 10 yrs) compared with marker-negative patients (mean 13.94 yrs, 95% CI 12.53 – 15.35 yrs).

Marker-positive patients with tumors<4cm had a lower probability of OS (60% *v* 92%) than marker-negative patients in the same group (marker-positive patients: mean OS 8.80 years, 95% CI 5.67- 11.93 years; marker-negative patients: mean OS 14.34 years, 95% CI 13.12 – 15.56 years, $p = 0.017$). Differences were not significant in patients with tumors ≥ 4cm. Similarly, a poorer DFS was observed in markers positive versus marker-negative patients with tumors <4cm (56% *v* 83%, $p = 0.015$), as well as for patients with tumors ≥4cm (27% vs. 100%, $p = 0.048$).

Table 5. Kaplan-Meier analysis of outcome of disease in FIGO stage IB in relation to SCC-Ag and CYFRA 21-1 levels, and lymph node status

Factors	Deaths/total	OS in yrs, mean (95% CI)	Recurrences/ total	DFS in yrs, mean (95% CI)
SCC-Ag -/CYFRA 21-1 -	2/20	13.98 (12.31 – 15.65)	3/20	13.26 (11.20 – 15.32)
SCC-Ag +/CYFRA 21-1 -	0/9	-	0/9	-
SCC-Ag -/CYFRA 21-1 +	0/6	-	0/6	-
SCC-Ag +/CYFRA 21-1 +	7/17	8.27 (5.84 – 10.71)	8/17	7.32 (4.64 – 10.00)
Marker -/Lymph node -	0/28	-	1/28	14.65 (13.51 – 15.78)
Marker +/Lymph node -	2/10	10.43 (7.80 – 13.06)	3/10	9.62 (6.73 – 12.51)
Markers -/Lymph node +	2/7	9.34 (5.82 – 12.85)	2/7	9.16 (5.41 – 12.90)
Markers +/Lymph node +	5/7	4.72 (1.55 – 7.89)	5/7	3.40 (0,01 – 6,93)

- = Negative; + = Positive.
Cutoff values: SCC-Ag, 1.1 µg/L; CYFRA 21-1, 1.4 µg/L; Marker + = SCC-Ag>1.1 µg/L and_CYFRA 21-1>1.4 µg/L; marker - = all others.

Marker-positive patients with negative lymph nodes had a lower OS than marker-negative patients in the same group (58% *v* 100%, $p = 0.015$); differences were not significant ($p = 0.115$) in lymph node-positive patients (Table 5 and Fig.2A). DFS (Table 5 and Fig.2B) was lower in marker-positive than in marker-negative patients without (58% *v* 91%, respectively; $p = 0.011$), and with lymph node involvement (17% *v* 68%, respectively; p = 0.042). None of the patients with negative lymph nodes and tumors <4cm died during the observation period. There were 2 recurrences in this group: a late recurrence (8.6 years) in the 24 marker-negative patients, and an early recurrence (1.6 years) in the 5 marker-positive patients.

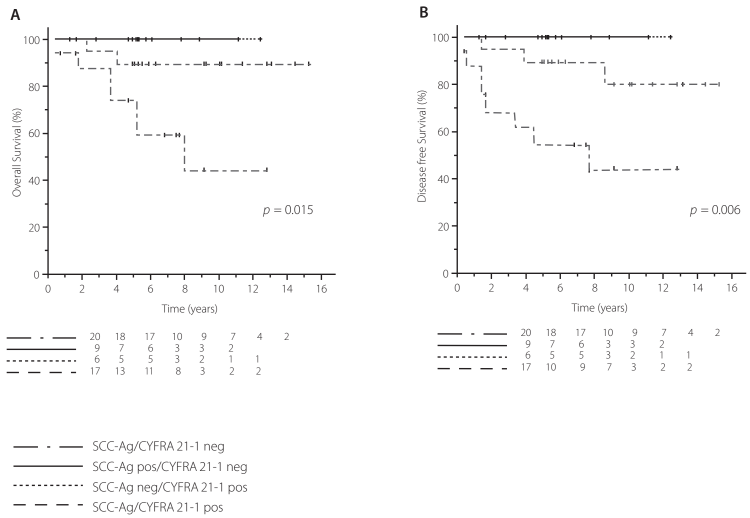

Figure 1. Kaplan Meier analysis showing OS (A), and DFS (B) related to SCC-Ag and CYFRA 21-1 levels in FIGO stage IB.

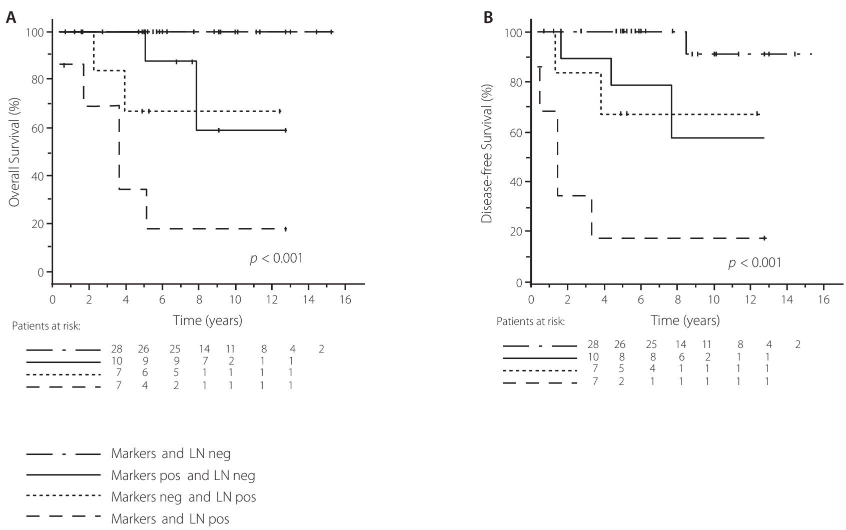

Figure 2. Kaplan Meier analysis showing OS (A) and DFS (B) related to SCC-Ag and/or CYFRA 21-1 negative (markers -) or SCC-Ag and CYFRA 21-1 positive (markers+), with or without lymph node (LN) involvement in FIGO stage IB. Differences remained significant after adjusting for tumor diameter <4 or ≥4 cm (p<0.001)

CA15-3 and CA125

In the total population, patients with CA15-3 > 40 U/mL had a lower OS (46% *v* 74%, $p = 0.013$) and DFS (44% *v* 70%, $p = 0.011$) probability compared to patients with CA15-3≤40 U/mL. Differences remained significant after adjusting for tumor diameter ($p = 0.021$ and $p = 0.028$, respectively), but not after adjusting for stage (IB vs. II), or lymph node status. Positive CA15-3 levels were associated with shorter OS and DFS in patients with tumors ≥4cm in the total population (23% *v* 65%, $p = 0.007$ and 29% vs. 64%, $p = 0.007$, respectively), but not in patients with tumors<4cm.
In the total population, patients with CA125 > 30 U/mL had a shorter OS and DFS compared to patients with CA125 ≤ 30 U/mL ($p = 0.044$ and $p = 0.032$, respectively). Differences in OS and DFS remained significant after adjusting for lymph node status ($p = 0.002$ and $p = 0.011$, respectively), but not for stage or tumor diameter. No significant difference in OS and DFS with respect to CA125 levels was observed in lymph node-negative patients. On the other hand, lymph node positive patients with raised CA125 (N 5) had a lower probability of OS ($p = 0.001$) and DFS ($p = 0.001$) than patients with CA125 below the cutoff (N 21) in the same group. However, these last results should be interpreted with caution as they are based on only 5 CA125 positive patients (Table 4): three of whom died within 1.7 years of primary treatment, and 2 were lost to follow up within the same period: 1 patient with no evidence of disease, while the other had a recurrence 6 months after primary treatment (see below).

Only 3 patients had concomitantly elevated levels of CA15-3 and CA125. All 3 patients (1 stage IB, lymph node positive; 2 stage IIB, 1 lymph node negative, the other lymph node positive) had disease recurrence within 6 months of primary treatment. Two of the patients died of cervical cancer within 9 months of primary treatment, the third patient (stage IB) was lost to follow up 9 months after primary treatment. In 2 of them, all four markers were elevated.

Kaplan Meier analysis of all 4 markers combined (SCC-Ag and CYFRA 21-1 positive or either CA 15.3 or CA 125 positive, N = 41) provided few additional information to that obtained with the combination of SCC-Ag and CYFRA 21-1 alone (results not shown).

Discussion

Cervical cancer incidence and mortality rates have fallen in wealthy countries in the last 40 years. Screening programs have led to women being diagnosed at an earlier stage of disease and at a younger age: In North America, nearly half of cases are diagnosed before the age of 35 [13]. Patient-tailored therapy is of paramount importance to be able to decrease morbidity and preserve reproductive organs in patients of childbearing age [14] without running the risk of treatment failure, since disease recurrence generally shows a poor response to salvage therapy. A study showed that only 12% of patients treated with a primary surgical approach for stage IB2 lesions (tumors> 4 cm) will have been adequately treated with surgery alone, the rest would be elegible for adjuvant therapy [15]. However, radical hysterectomy combined with pelvic radiotherapy is associated with a significant risk of complications [16], which could be partially avoided by treating high-risk patients with primary chemotherapy and radiation alone [17]. Pretreatment levels of serum tumor markers may be indicators of occult disease providing additional information to that obtained by imaging modalities and surgical staging. Furthermore, they constitute a noninvasive, simple, easy-to-implement and low-cost procedure that could prove useful not only in developing countries but also within Europe. In a recent study, a striking contrast was noted in cervical cancer standardised incidence (9.5 *v* 16.7) and mortality rates (4.9 *v* 10.7) between the 15 old and the 10 new European Union member states, indicating that cervical cancer remains a considerable health problem in Europe [18].

Elevated pretreatment serum SCC-Ag levels have been associated with advanced disease and bad prognosis [19 - 24], whereas others found no independent prognostic value for SCC-Ag in early stage cervical cancer [25, 26]. Similar to SCC-Ag, pretreatment serum levels of CYFRA 21-1 are significantly related to tumor stage, tumor size and the presence of either lymph node metastases or parametrial involvement, but they have no independent prognostic value [26 - 29]. In SCC of the cervix, a significant association between elevated pretreatment CA125 levels and the presence of lymph node metastases has been reported [19, 30], as well as vascular spread of the disease [31].

In agreement with the literature, in the present study SCC-Ag, CYFRA 21-1 and CA 125 levels were significantly associated with FIGO stage (IB vs. IIB) and tumour size, whereas CA 15-3 was only significantly associated with stage. An association with lymph node status was found only for SCC-Ag levels, in the total population and in stage IB. Similar associations were observed in the contingency tables (Table 4).

With the exception of CA125, all markers were significantly associated with OS and DFS in univariate analysis, but only CYFRA 21-1 and CA15-3 had independent prognostic value, albeit only for DFS, in multivariate analysis (Table 3).

In most studies, cutoff values of tumor markers for diagnosis have been established in relation to healthy cohorts, and thus may not necessarily be useful as prognosticators for outcome. The clinical cutoff values defined in the present study corresponded to the diagnostic cutoff values proposed by the manufacturers for CYFRA21-1, did not greatly differ for CA125 and CA15-3, but was much lower for SCC-Ag. The use of CYFRA21-1 in cervical SCC has been relegated in favor of SCC-Ag, but our findings suggest that the two markers provide complementary information. A concomitant elevation of SCC-Ag and CYFRA 21-1 above the clinical cutoff value defined a group of patients with poor prognosis, not only within the total population but also within FIGO stage IB. Lymph node positive patients with elevated SCC-Ag and CYFRA 21-1 had even a worse outcome. Of more clinical interest, both markers above the cutoff identify a group of stage IB lymph node- negative patients with a poor prognosis, suggesting the presence of occult disease. An interplay between marker levels, and extent and outcome of disease is suggested by the observation that in the latter group disease outcome was similar to marker-negative patients with lymph node involvement.

The only study on CA15-3 and cervical cancer found a weak association between pretreatment CA15-3 levels and response to chemotherapy [6]. In the present study, CA15-3 had independent prognostic value for DFS, and positive levels were associated with positive lymph nodes. The three women with concomitant elevation of CA15-3 and CA125 died. The low frequency of elevated levels in FIGO stage IB suggests that CA125 and CA15-3 are marginally useful in early stage cervical cancer, but should be evaluated as prognostic factors in locally advanced disease where they may be of use in the future when new treatment modalities are being developed for this group of patients.

In conclusion, a panel of SCC-Ag and CYFRA 21-1 may provide information on the presence of occult disease in early stage SCC of the uterine cervix. Its use as an additional tool to establish patient-tailored therapy should be analyzed in prospective studies. Additionally, CA125 and CA15-3 may have prognostic value in locally advanced cervical cancer.

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3

SCC-Ag, lymph node metastases and sentinel node procedure in early stage squamous cell cervical cancer.

SCC-Ag, lymph node metastases and sentinel node procedure in early stage squamous cell cervical cancer.

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Abstract

Objectives: We analyzed pretreatment SCC-Ag levels, lymph node (LN) status and disease outcome in early stage squamous cell (SCC) cervical cancer. Methods: Serum SCC-Ag was measured before primary treatment in 91 patients (FIGO stage IB1 72, IB2 10, and IIA 9). Of these, 58 underwent laparoscopic sentinel lymph node (SLN) procedure followed by pelvic lymphadenectomy.

Results: No false negative SLN were observed. SCC-Ag levels were higher in patients with positive LN compared to patients with negative LN ($p = 0.010$), but no difference was found in the SLN patients ($p = 0.344$). The accuracy to predict LN metastases of SCC-Ag at ROC established cutoff of 1.65 ng/mL and 5.5 ng/mL was 76% and 78%, respectively, in stage IB1, and 53% and 79%, respectively, in stages IB2 + IIA. Whereas no deaths were observed in patients with negative LN and negative SCC-Ag levels (at previously established cutoff of 1.1 ng/mL), overall survival (OS) for patients with negative LN but elevated SCC-Ag was similar to that of patients with positive LN, irrespective of their marker levels (Kaplan Meier analysis of all patients and in stage IB1, $p = 0.002$ and $p = 0.026$, respectively).

Conclusions: SCC-Ag (>1.65 ng/mL) can predict LN metastases more accurately in stage IB1 than in stage IB2 + IIA. Since SCC-Ag levels above 1.1 ng/mL are already associated with a poor prognosis, the marker seems to identify a subgroup of LN negative patients with occult disease that may benefit from full lymphadenectomy following a SLN procedure.

Introduction

Cervical cancer is the second most common cancer in women worldwide, and accounts for 9% of female cancer deaths. It is much more common in developing than in developed countries, reflecting the effect of screening programs on cervical cancer incidence in the latter. Age-adjusted survival varies between 61% and 41% in developed and developing countries, respectively [1].

The current International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer [2] does not take into account pelvic LN status, which is a major prognostic factor for disease outcome [3, 4]. To establish a better mode of primary treatment and limit the morbidity associated with the need of pelvic radiotherapy after radical hysterectomy, imaging techniques and surgical staging procedures are used to assess extent of local disease and LN status [5].

Approximately 80% of cervical cancer cases are SCC carcinomas. SCC-Ag is the serum tumor marker most commonly used for clinical monitoring of SCC cervical cancer [6-9]. Elevated pre-treatment SCC-Ag levels correlate with extent of disease (tumor diameter, depth of cervical stromal invasion (DSI), lymphovascular space invasion (LVSI), parametrial involvement (PI) and LN metastasis), and, in some studies, with bad prognosis [10-18].

The present study investigates whether pretreatment SCC-Ag levels correlate with LN status defined by laparoscopic SLN biopsy and/or pelvic lymphadenectomy, and analyzes its utility as an adjunct to SLN procedures. Furthermore, we examined the prognostic value of pretreatment SCC-Ag levels as a possible means of defining patients at high risk of recurrence that may benefit from primary therapy other than that warranted by current clinical parameters and staging, i.e. more extensive surgery or chemoradiation instead of surgery.

Materials and methods

Serum samples and study population

SCC-Ag was measured routinely before primary treatment in 91 patients with SCC cervical cancer (FIGO stage IB1 72, IB2 10, and IIA 9) treated at the VU University Medical Center between 1996 and 2006. Patients with a prior or concomitant history of malignancy were excluded from the study. All patients underwent full (laparoscopic) lymphadenectomy, which was preceded by laparoscopic SLN procedure in 58 patients, as previously described [19]. In summary, patients received a pre-operative intracervical injection of technetium-99m colloidal albumin and blue dye, SLN were identified and separately removed via laparoscopy. If SLN were negative for malignant cells, a laparoscopic pelvic LN dissection followed by radical hysterectomy (abdominal or vaginal) was performed. If SLN showed malignant cells, full LN dissection was performed up to the next tumor free level, and the patient received radiotherapy or chemoradiation therapy. Table 1 lists the clinicopathological characteristics of the patients and their primary treatment. Information on patient outcome was available in all patients. The principal events analyzed were recurrence and death. Disease-free survival (DFS) was defined as the time elapsed between the start of primary treatment and the first reappearance of cervical cancer at any site, or the date of the last visit for patients with no evidence of disease. OS was defined as the time elapsed between primary treatment and death, or the date of the last visit for all other patients. All deaths were cervical cancer related.

Blood samples were obtained by venous puncture, allowed to clot at room temperature, centrifuged, and analyzed.

Procedures followed were in accordance with the Helsinki declaration of 1975, as revised in 1983, and in accordance with the guidelines for research of our institute.

SCC-Ag assay

SCC-Ag [20] was analyzed routinely at each patient's visit to the outpatient clinic with a microparticle enzyme-immunoassay system (IMx, Abbott Diagnostics, Chicago, IL). The cutoff level recommended by the manufacturers is 1.5 ng/mL.

Statistical methods

Statistical analysis was performed using SPSS software (Version 15.0, SPSS Inc, Chicago, IL.). SCC-Ag levels and LN status were evaluated by the receiver-operating characteristic (ROC) method [21], and the diagnostic value calculated for SCC-Ag cutoffs extracted from the curve. The "best" cutoff was determined by maximization of the sum of the sensitivity and specificity. Assay results in patient groups were analyzed using the Mann-Whitney *U* test. The distribution of marker levels above or below the cutoffs was analyzed in contingency tables according to clinicopathological characteristics with the Pearson χ^2 test or, when the sample size was small (any one cell with expected count<5), the Fisher's exact test. Univariate and multivariate analysis of DFS and OS was performed in the total population using the Cox proportional hazards regression model [22]. The model

Table 1. Clinicopathological characteristic of the patients with SCC cervical cancer

Characteristics	N	FIGO stage		
	Total (N = 91)	IB1 (N = 72)	IB2 (N = 10)	IIA (N = 9)*
Median age, years (range)	42 (23 – 89)	42 (25 – 89)	48 (23 – 74)	41 (29 – 75)
Histological grade				
– I	8	7	1	0
– II	44	32	6	6
– III	38	32	3	3
– Not known	1	1	0	0
DSI†				
– ≤ 15 mm	56	50	3	3
– > 15 mm	17	7	5	5
– Not known	5	5	0	0
LVSI†				
– Absent	55	46	6	3
– Present	20	14	2	4
– Not known	3	2	0	1
PI†				
– Absent	73	59	6	8
– Present	5	3	2	0
Resection margins†				
– Free	70	60	5	5
– Not free	7	1	3	3
– Not known	1	1	0	0
LN metastases:				
– Absent	66	55	7	4
– Present	25	17	3	5
SLN procedure	58			
– SLN Negative	44	38	5	1
– SLN Positive	12	12	0	0
– No SLN found	2	2	0	0
Primary treatment:				
– Radical hysterectomy	61	53	5	3
– Rad. hysterectomy and radiotherapy	8	6	0	2
– Rad. hysterectomy and chemoradiation	9	3	3	3
– Radiotherapy	3	2	0	1
– Chemoradiation	10	8	2	0
Recurrences, N (%)	17 (18.7)	8 (11.1)	4 (40.0)	5 (55.6)
Deaths, N (%)	14 (15.4)	6 (8.3)	4 (40.0)	4 (44.4)
Median DFS, years (range)	4.2 (0.3 – 10)	4.3 (0.5 – 10)	3.6 (0.3 – 7.5)	3.2 (0.3 – 10)
Median OS, years (range)	4.5 (0.5 – 10)	4.4 (1.0 – 10)	4.3 (1.1 – 7.5)	5.2 (0.5 – 10)

*Three patients had tumors < 4 cm; †radical hysterectomy, N = 78. Abbreviations: DSI, depth of cervical stromal invasion; LSVI, lymphovascular space invasion; PI, parametrial involvement; DFS, disease-free survival; OS, overall survival.

included as potential predictors the following clinicopathological features: age, histological grade (I + II *vs.* III), FIGO stage (IB1 *vs.* IB2 + IIA), LN involvement (negative *vs.* positive), tumor diameter (<4cm *vs.* ≥4cm), and SCC-Ag levels entered as a continuous variable. PI (absent *vs.* present), DSI (≤15mm *vs.* >15mm), LVSI (absent *vs.* present) and resection margins (free *vs.* not free) were added to the model for evaluation in the patient population that underwent radical surgery (N = 78). The probability of DFS and OS in relation to a previously established SCC-Ag cutoff of 1.1 ng/mL [23] and LN status was analyzed using the Kaplan-Meier method [24], and univariate comparisons between subgroups were made using a two-tailed log-rank test; tests with p values ≤ 0.05 were considered statistically significant.

Results

SCC-Ag levels and clinicopathological characteristics

SCC-Ag levels in the study population are shown in Table 2. SCC-Ag levels did not differ significantly between stage IB2 and IIA. Stage IB1 patients with positive LN, but not stage IB2 or IIA patients, had significantly higher levels of SCC-Ag than patients with negative LN (p = 0.044). Distribution of negative or positive SCC-Ag levels in relation to clinicopathological characteristics and disease outcome are displayed in Table 2.

The value of SCC-Ag to discriminate between patients with negative and positive LN was analyzed by receiver-operating characteristics (ROC) curves in the total population (Fig. 1A) and in stage IB1 (Fig. 1B).

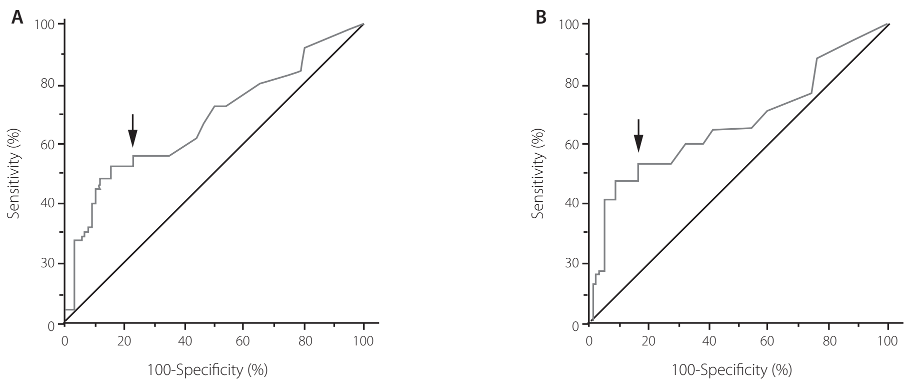

Figure 1 Receiver-operating characteristic (ROC) curves for SCC-Ag comparing data obtained from patients with negative or positive LN in (A) the total population, and (B) stage IB1. The area under the curve is 0.675 (standard error 0.068), p = 0.010 for (A), and 0.661 (standard error 0.085), p = 0.045 for (B). The "best" cutoff point (↓) corresponds to a SCC-Ag level of 1.65 ng/mL.

Table 2. SCC-Ag levels in relation to tumor characteristics and disease outcome

		SCC-Ag (ng/mL)		SCC-Ag >1.1 ng/mL		SCC-Ag >1.65 ng/mL	
	N	**Median (range)**	***p* value***	**N (%)**	***p* value†**	**N (%)**	***p* value†**
Total	91	1.1 (0.3 – 60.8)		44 (47.3)		30 (32.2)	
FIGO stage							
– IB1	72	0.8 (0.3 – 12.0)	<0.001	28 (38.9)	0.008	18 (25.0)	0.023
– IB2 + IIA	19	2.7 (0.5 – 60.8)		15 (78.9)		11 (57.9)	
Histological grade							
– I	8	0.9 (0.3 – 3.8)	ns	3 (37.5)	ns	1 (12.5)	ns
– II	44	1.0 (0.3 – 60.8)		20 (45.5)		12 (27.3)	
– III	38	1.3 (0.3 – 9.2)		20 (52.6)		16 (42.1)	
Tumor diameter							
– <4cm	75	0.9 (0.3 – 12.0)	<0.001	30 (40.5)	0.007	18 (24.3)	0.001
– ≥4cm	16	3.0 (0.5 – 60.8)		13 (76.5)		11 (64.4)	
DSI							
– ≤ 15 mm	56	0.7 (0.3 – 12.0)	<0.001	16 (28.6)	<0.001	10 (17.9)	<0.001
– > 15 mm	17	3.0 (0.5 – 60.8)		14 (82.4)		11 (64.7)	
LVSI							
– Absent	55	0.7 (0.3 – 12.0)	ns	21 (38.2)	ns	14 (25.5)	ns
– Present	20	1.2 (0.3 – 60.8)		10 (50.0)		6 (30.0)	
PI							
– Absent	73	0.8 (0.3 – 10.0)	0.001	29 (39.7)	0.013	18 (24.7)	0.021
– Present	5	11.0 (1.4 – 60.8)		5 (100.0)		4 (80.0)	
Resection margins							
– Free	70	0.7 (0.3 – 12.0)	0.001	26 (37.1)	0.002	16 (22.9)	0.014
– Not free	7	6.0 (1.2 – 60.8)		7 (100.0)		5 (71.4)	
LN metastases							
– Absent	66	0.9 (0.3 – 45.0)	0.010	28 (42.4)	ns	15 (22.7)	0.002
– Present	25	2.1 (0.3 – 60.8)		15 (60.0)		14 (56.0)	
SLN							
– Negative	44	0.7 (0.3 – 12.0)	ns	14 (31.8)	ns	10 (22.7)	ns
– Positive	12	1.1 (0.3 – 4.7)		6 (50.0)		5 (41.7)	
Recurrences							
- no	74	0.9 (0.3 – 45.0)	0.003	30 (40.5)	0.014	20 (27.0)	0.039
- yes	17	2.8 (0.3 – 60.8)		13 (76.5)		9 (52.9)	
Deaths							
- no	77	0.9 (0.3 – 45.0)	0.004	32 (41.6)	0.018	21 (27.3)	0.027
- yes	14	2.7 (0.3 – 60.8)		11 (78.6)		8 (57.1)	

Mann-Whitney *U* test; †Pearson χ^2 test. Abbreviations: ns, not significant; DSI, depth of cervical stromal invasion; LSVI, lymphovascular space invasion; PI, parametrial involvement.

The "best" cutoff was 1.65 ng/mL in both cases. SCC-Ag values of 3.95 ng/mL and 5.5 ng/mL corresponded to a specificity of 90% and 95%, respectively, in the total population. The diagnostic value for LN involvement of these three cutoffs was analyzed in stage IB1, and in stages IB2 + IIA (Table 3). The specificity for LN involvement of the 1.65 ng/mL cutoff was much higher in stage IB1 than in stages IB2 plus IIA; this was reflected in the corresponding likelihood ratios. The accuracy of the 1.65 ng/mL cutoff to predict LN involvement in stage IB1 was almost the same as that of a cutoff of 5.5 ng/mL in stage IB2 plus IIA (Table 3).

Table 3. Diagnostic value of SCC-Ag for LN involvement in stage IB1, and in stages IB2 + IIA

	IB1 (N 72)			IB2 + IIA (N 19)		
SCC-Ag, cutoff	1.65 ng/mL	3.95 ng/mL	5.5 ng/mL	1.65 ng/mL	3.95 ng/mL	5.5 ng/mL
Sensitivity	53%	18%	12%	63%	63%	63%
Specificity	84%	95%	98%	46%	73%	91%
PPV	50%	50%	67%	46%	63%	83%
NPV	85%	79%	78%	63%	73%	77%
Accuracy	76%	76%	78%	53%	68%	79%
LR, 95% CI	3.3 1.3 – 8.3	3.6 0.2 – 55.7	6.0 0.1 – 432.7	1.2 0.4 – 3.4	2.3 0.6 – 8.9	7.0 0.8 – 59.7

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio (sensitivity/1−specificity); CI, confidence interval.

Laparoscopic SLN procedure was performed in 58 patients, followed by full lymphadenectomy to evaluate the accuracy of the results obtained and to treat patients according to common guidelines. All 44 patients with negative SLN had negative nodes at subsequent lymphadenectomy. From the 12 patients with positive SLN, 9 had no further positive LN, the other three had 1, 5 and 6 additional positive LN. No SLN could be detected in two patients: one (SCC-Ag 0.5 ng/mL) was LN negative, and the other (SCC-Ag 2.1 ng/mL) had 2 positive LN detected by lymphadenectomy. SCC-Ag levels did not differ significantly between patients with negative or positive SLN (Table 2). ROC curve analysis in this smaller group of patients was less informative than in the total population (results not shown).

SCC-Ag levels and outcome of disease

Cox regression analysis of DFS and OS in relation to disease characteristics and SCC-Ag levels was performed in the total population (Table 4). Age and grade were not significantly associated with DFS and OS in univariate analysis. Multivariate analysis identified stage and LN status as the only independent predictors for DFS and OS. PI, LVSI and resection margins, but not DSI, were significantly associated with DFS and OS in univariate analysis in the population that underwent radical hysterectomy. Only the state of the resection margins was an independent predictor for DFS and OS, together with stage and LN status (results not shown).

A clinical SCC-Ag cutoff level of 1.1 ng/mL defined in an earlier retrospective study by maximizing the log-rank statistics for OS in the total population [23] was confirmed as the most informative cutoff in the present prospective study. Kaplan Meier analysis of SCC-Ag ≤ 1.1 ng/mL (SCC-Ag negative) or > 1.1 ng/mL (SCC-Ag positive) in the total population showed a lower probability of DFS (68% *vs.* 91%, p = 0.013) and OS (55% *vs.* 93%, p = 0.031) for patients with positive than for patients with negative SCC-Ag. These differences did not remain significant after adjusting for stage (DFS, p = 0.179; OS, p = 0.100). After adjusting for LN status, differences remained significant for DFS (p = 0.038), but not for OS (p = 0.104).

Table 4. Disease characteristics and SCC-Ag levels evaluated for an association with outcome of disease in the total population (n = 91)

	OS		**DFS**	
Factors	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Univariate analysis				
Stage IB1 *vs.* IB2 + IIA	4.46 (1.50 – 13.22)	0.004	5.11 (1.97 – 13.25)	<0.001
LN neg. *vs.* pos.	5.32 (1.78 – 15.90)	0.001	3.29 (1.27 – 8.55)	0.009
Tumor diameter <4cm *vs.* ≥4cm	3.79 (1.29 – 11.16)	0.010	4.70 (1.81 – 12.19)	<0.001
SCC-Ag (ng/mL)	1.03 (1.00 – 1.07)	0.031	1.03 (1.00 – 1.07)	0.019
Multivariate analysis				
Stage IB1 *vs.* IB2 + IIA	3.42 (1.12 – 10.45)	0.031	4.39 (1.67 – 11.56)	0.003
LN neg. *vs.* pos.	4.27 (1.40 – 13.00)	0.011	2.66 (1.01 – 7.00)	0.048
HR, hazard ratio				

Kaplan Meier analysis of OS and DFS in the total population and in stage IB in relation to SCC-Ag and LN status divided into four groups (-/-, +/-, -/+, and +/+, respectively), is displayed in Fig. 2. No deaths and only one recurrence was observed in the 38 patients with negative LN and SCC-Ag (-/-), of whom 37 were stage IB1. In the total population (Fig. 2A and 2C), OS (p = 0.025) and DFS (p = 0.011) probability was higher for patients with negative SCC-Ag and LN (-/-) than for patients with positive SCC-Ag and negative LN (+/-). The same was observed in stage IB1 (Fig. 2B and 2D), but differences did not reach significance (OS, p = 0.087; DFS, p = 0.085). In stage IB1, outcome of disease of patients with positive SCC-Ag and negative LN (+/-) did not differ significantly from that of patients with positive LN with either negative (-/+) or positive SCC-Ag (+/+).

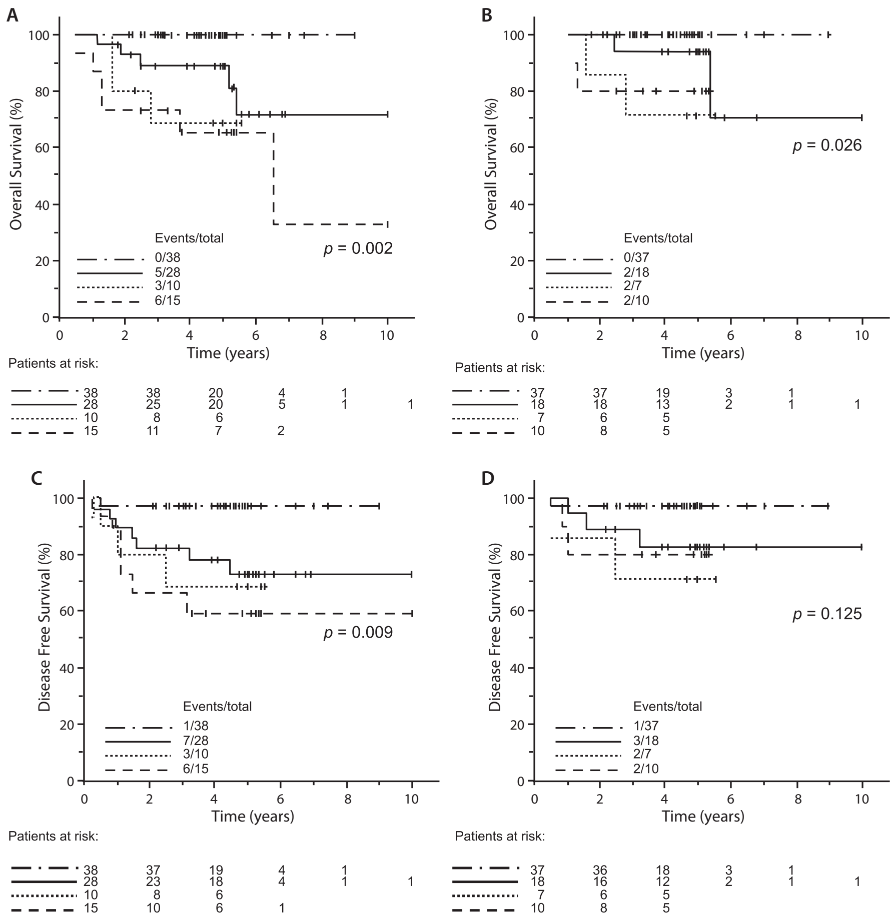

Figure 2 Kaplan Meier graphs of OS (A and B), and DFS (C and D) in relation to SCC-Ag and LN status in the total population (A and C) and in stage IB1 (B and D). — · — · SCC-Ag negative and LN negative (–/–); ———— SCC-Ag positive and LN negative (+/–); ············ SCC-Ag negative and LN positive (–/+); – – – – SCC-Ag positive and LN positive (+/+).

Discussion

Radical surgery and radiotherapy have equal cure rates in stage IB-IIA SCC cervical cancer, but a combination of them results in increased morbidity [25]. The objective of LN mapping is to reject radical surgery in favor of chemoradiation in case of tumor positive nodes. With appropriate detection techniques, the false negative rate of SLN biopsy is very low [26], and. it may become possible to rely on the SLN and avoid full lymphadenectomy in all patients. However, a recent multicenter study found an acceptable sensitivity for the SLN concept only in patients with tumors ≤2cm, and concluded that systematic lymphadenectomy cannot be omitted at the moment [27]. Furthermore, pathologic evaluation of negative SLN should address micrometastatic disease, since it has been shown that metastatic disease may be detectable only at a molecular level [28], and this may have an influence on prognosis [4]. Micrometastases are identifiable in histologically negative LN in 15% of early-stage cervical cancer patients, a frequency which approximates the recurrence rate for patients with negative LN [29]. A tumor marker that could identify a subgroup at higher risk, particularly within the SLN-negative cases, would be useful for decision making. Since elevated marker levels are associated with a worse prognosis, node negative patients with small tumors and raised SCC-Ag may benefit from a full lymphadenectomy to clear submicroscopic disease or correct for a false negative SLN.

In agreement with previous reports [10-16], we found a correlation between clinicopathological tumor characteristics and SCC-Ag levels. Although SCC-Ag levels correlated with LN status, the overall clinical performance of the marker to predict LN involvement was poor. The differences in accuracy and likelihood ratio of the "best" cutoff value (1.65 ng/mL) between stage IB1 and stages IB2 + IIA probably reflect the effect of tumor size on SCC-Ag levels in the latter. Because of smaller tumors in stage IB1, an elevated marker is more likely to reflect the presence of LN metastases in it than in higher stages. Thus, 53% of stage IB1 patients with SCC-Ag>1.65 ng/mL had positive LN, as opposed to 16% of the patients with values ≤ the cutoff. However, in stages IB2 + IIA the percentage of patients with positive LN and values > or ≤1.65 ng/mL was almost the same (63% and 55%, respectively). In IB1, a cutoff of 5.5 ng/mL was highly specific for LN involvement (98%), but the corresponding sensitivity was very low (12%). This is reflected in the wide confidence interval of the likelihood ratio. Nevertheless, SCC-Ag assessment may contribute to identify a subgroup of IB1 cervical cancer patients at high risk for LN involvement, and could serve as an adjunct to SLN, to define patients that would benefit from a full lymphadenectomy. Further research is needed in a larger group of patients treated within a shorter time span, to avoid the possible bias of changes in surgical techniques.

Stage and LN status were the most important prognostic factors for outcome of disease in the present study. SCC-Ag levels have been associated to disease outcome, but the cutoff levels employed vary from study to study. A SCC-Ag cutoff value of 3.0 ng/mL was significantly associated with disease outcome in patients with SCC cervical cancer stages IA2 to IIB [14]. In early stage SCC cervical cancer, preoperative serum SCC-Ag levels>1.9 ng/mL correlated significantly with the need of postoperative radiotherapy [16]. In stage IB1 patients with no indication for adjuvant radiotherapy, recurrences were more frequent in patients with elevated pre-treatment SCC-Ag (15%) than in patients with normal SCC-Ag levels (1.8%) [16]. A cutoff level for SCC-Ag of 1.1 ng/mL defined as being associated with a bad prognosis in a previous retrospective study [23], was confirmed as the most informative in the present prospective study. Although SCC-Ag positive patients showed a lower DFS and OS in the total population, these differences were not significant when adjusting for stage, suggesting that elevated SCC-Ag reflects tumor size, and thus poor outcome. In patients with negative LN, however, elevated SCC-Ag identifies a subset of patients with poor disease outcome, and is possibly indicating the presence of occult disease (Fig. 2).

More reliable information may be obtained by combining SCC-Ag with other markers. Recently, we showed that SCC-Ag and CYFRA 21-1 (cytokeratin 19) together identify patients with early stage cervical cancer with poor disease outcome independent of stage, LN status and tumor size [23]. Cytokeratin 19 identifies LN micrometastases [28], and elevated marker levels may be related to their presence.

In conclusion, SCC-Ag correlates with both OS and DFS, most likely as a reflection of extent of disease. In stage IB1, high SCC-Ag levels are strongly suspicious of the presence of LN metastases, but lower values do not exclude them. At present studies suggest that a SLN procedure, with the advantage of reduced morbidity compared to full lymphadenectomy, may be adequate, sufficient and safe in early stage cervical carcinoma. Nevertheless, patients with negative SLN but elevated SCC-Ag may benefit from full lymphadenectomy to address occult disease. Whether this subgroup of patients would benefit from chemoradiation rather than surgery, to avoid the necessity of a combination of radical treatments, should be evaluated in clinical trials.

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4

Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review.

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Abstract

Objective. The aim of this study was to systematically review the diagnostic performance of Sentinel Node (SN) detection for assessing the nodal status in early stage cervical carcinoma, and to determine which technique (using blue dye, Technetium-99m colloid (^{99m}Tc), or the combined method) had the highest success rate in terms of detection rate and sensitivity.

Methods. A comprehensive computer literature search of English language studies in human subjects on Sentinel Node procedures was performed in MEDLINE and EMBASE databases up to July 2006. For each article two reviewers independently performed a methodological qualitative analysis and data extraction using a standard form. Pooled values of the SN detection rate and pooled sensitivity values of the SN procedure are presented with a 95% confidence interval (95% C.I.) for the three different SN detection techniques.

Results. We identified 98 articles, and twenty-three met the inclusion criteria, comprising a total of 842 patients. Ultimately, twelve studies used the combined technique with a sensitivity of 92% (95% C.I.: 84-98%). Five studies used 99mTc-colloid, with a pooled sensitivity of 92% (95% C.I.: 79-98%; p=0.71 vs. combined technique), and four studies used blue dye with a pooled sensitivity of 81% (67-92%, p=0.17 vs. combined technique).

The SN detection rate was highest for the combined technique: 97% (95% C.I.: 95-98%), vs. 84% for blue dye (95% C.I.: 79-89%; p<0.0001), and 88% (95%C.I.: 82-92%, p=0.0018) for ^{99m}Tc colloid.

Conclusion. SN biopsy has the highest SN detection rate when ^{99m}Tc is used in combination with blue dye (97%), and a sensitivity of 92%. Hence, according to the present evidence in literature the combination of ^{99m}Tc and a blue dye for SN biopsy in patients with early stage cervical cancer is a reliable method to detect lymph node metastases in early stage cervical cancer.

Introduction

Uterine cervical cancer remains the third most common female malignancy worldwide, despite a gradual fall in its frequency in western countries [1]. This disease continues to be diagnosed in locally advanced stages despite screening in many countries. In western countries half of patients are detected through symptoms such as abnormal vaginal bleeding and vaginal discharge, and the remaining ones by screening [2]. The Federation Internationale de Gynecologie et d'Obstetrique (FIGO) clinical staging system does not include evaluation of lymph node involvement. However, lymph node status remains the single most important prognostic factor in early stage cervical cancer [3-6].

Systematic lymph adenectomy is the standard technique currently used to detect lymphatic spread. Lymph node involvement is common, up to 27% in early stages [7-14].

For patients with early stage cervical cancer in the Western world radical hysterectomy and pelvic lymph node dissection is the treatment of choice [15]. In the event of proven lymphatic metastases, (chemo) radiation is the primary treatment [16].

Approximately up to 25% of operable cases will eventually require additional chemo-radiation therapy (8). Patients with proven microscopic lymph node metastases derive no benefit from lymph adenectomy in invasive cervical cancer, so complete pelvic lymph node dissection seems unnecessary for some cases when radiotherapy is offered [10;17-21].

In the search of more accurate preoperative diagnostics, cross-sectional imaging modalities such as computed tomography and magnetic resonance imaging have been proposed [22]. Unfortunately, all these imaging techniques notoriously fail to reliably detect lymph node metastases [23].

Since the introduction by Cabanas of the sentinel node concept to reduce the complication rate of lymphadenectomy, it has been proven feasible to detect lymph node metastasis on the basis of selective lymph node dissection [24]. When nodal metastases occur, the sentinel lymph node will be initially involved. According to the sentinel node hypothesis, histologically tumor negative sentinel lymph nodes predict that also the remaining lymph nodes will be free of tumor [25; 26]. This hypothesis has proven to be true in melanoma and breast cancer and is currently being studied in the treatment of other malignancies, such as cervical and vulvar cancer [12; 27-30].

The aim of this systematic review is to summarize the available evidence on the sensitivity of the sentinel node biopsy in cervical cancer, and to explore whether its feasibility is a function of the SN localizing technique.

Materials and methods

Data sources and study selection

A comprehensive computer literature search of English language studies in human subjects was performed to identify articles on the diagnostic performance of SN and cervical carcinoma compared with histopathology as reference standard.

The MEDLINE and EMBASE databases to July 2006 were searched for the following terms: "cervix neoplasm, sentinel node" as medical subject headings (MeSH) and "specificity/or false negative/or accuracy" as text words. The list of articles was supplemented by extensive crosschecking of the reference lists of the identified articles. Review articles, letters, comments, conference proceedings, unpublished data and case reports were not selected for this review.

Studies were included when all of the following inclusion criteria were met: (1) minimum sample size of 10 patients; (2) for analysis of sensitivity of SN: presence of gold standard, defined as a clearly described histopathology analysis of specimens obtained by laparoscopic surgery, laparotomy or biopsy; (3) sufficient data to construct 2 × 2 contingency tables (cells labelled as true positives, false positives, true negatives, and false negatives) or sufficient detail to reconstruct a SN detection rate; (4) the use of a radioactive tracer and/or blue dye in the sentinel node procedure; (5) majority (>80%) of included patients with early stage cervical cancer (FIGO I-IIA). The exclusion criterion was an overlap in patient data (duplicate publication), in which case the more recent article with most patients was included with an adequate description of study population.

Data extraction

The methodological quality of each article was independently assessed by two reviewers (BT, JL) in terms of internal and external validity, based on the Cochrane Methods Group in Screening and Diagnostic Tests [31], modified for studies concerning SN detection in patients with early stage cervical carcinoma (Table 1). The internal validity items focus on the validity of the reference test, whether this reference test was applied uniformly and independently or interpreted, as well as on the type of study design. The external validity items evaluate the applicability of the results in terms of the type of patient population and spectrum, demographics, the inclusion/exclusion criteria, the knowledge of previous test/clinical information which might influence interpretation, and the index test characteristics. Items were scored as positive, negative or unclear.

We also recorded whether data were reported in a per patient or per side analysis (for lymph node metastases). For each study sensitivity (tumor positive sentinel nodes divided by the total number of tumor positive lymph nodes) was calculated from the 2 × 2 tables for detection of lymph node involvement. Furthermore, we extracted the SN detection rate: i.e. the percentage of patients in whom a SN was found. The following methodological design criteria were scored for all included studies (Table 2): patient selection (consecutive or non-consecutive), interpretation of results (blinded or not blinded), method of verification (partial verification or complete), method of data collection (prospective, retrospective or unknown), description of study population, diagnostic test(s), and reference test (sufficient or insufficient). The reference test (histopathology of lymph nodes dissected by surgery) and the diagnostic test SN had to be described with sufficient detail to allow for replication, validation, and generalization of the study. If clear definitions of test results were mentioned in the text it scored positive.

For the description of the study population (apart from the criteria mentioned before) at least the following characteristics should be described: age of participants, histological proven cervical cancer and FIGO stage classification.

Data analysis

Data were analyzed according to the guidelines for meta-analyses evaluating diagnostic tests [32]. The sensitivity of the SN procedure was determined from the number of true positive (TP), and false negative (FN) results from the 2 x 2 contingency table of the individual studies. Studies that did not present patients with tumor positive sentinel nodes were excluded from statistical pooling of the sensitivity. However, these studies were included for pooling of the SN detection rate. Heterogeneity of the sensitivity and SN detection rate was tested using the Chi-square test. We performed a subgroup analysis for the three SN detection techniques: ^{99m}Tc-colloid, blue dye and the combined technique. In case of persisting heterogeneity between studies we used a random effect model for pooling of data, and a fixed effect model in case of homogeneity. Pooled data are presented with 95% confidence intervals (95% C.I.). Finally, pooled estimates of sensitivity and SN detection rate of the three different SN detection techniques (blue dye, ^{99m}Tc-colloid and the combined technique) were compared with a Z-test. A p-value < 0.05 was considered as significant.

Table 1. Criteria List Used to Assess Methodological Quality of the Studies

Criteria of Validity	Positive Score
Internal validity	
1. Valid reference test	Histology
2. Consecutive patient selection	Mentioned in publication
3. Blinded interpretation of results (pathology)	Mentioned in publication
4. Prospective study	Mentioned in publication
External validity	
5. Stage of disease (FIGO)	Mentioned in publication
6. Spectrum of disease	Percentage of stages Ia1-IIa as calculated
7. Demographic information	Mean age information given
8. Inclusion criteria described	Mentioned in publication
9. Exclusion criteria described	Mentioned in publication
10. Avoidance of selection bias	Consecutive series of patients
11. Description of SN criteria	Mentioned in publication
12. Technique SN detection described used	Blue dye and/or radioactive tracer, localisation and amount described
13. Scintigraphy	Mentioned in publication
14. Localization of SN (and/or bilateral SN) described	Mentioned in publication

Results:

Literature search

The search strategy yielded 62 publications in EMBASE and 56 in MEDLINE; 22 studies were identified in both databases. From the resulting 78 studies, 35 were excluded after reviewing the information provided in the title and abstract. Reviewing the full articles of the 43 remaining studies resulted in exclusion of another 18 studies because of ineligibility [17] and duplicate publication (1) [33]. For the meta-analysis of the sensitivity we excluded two studies due to absence of data regarding the histopathological procedure [27; 34], but these studies were appropriate for SN detection rate meta-analysis. Two studies had no patients with tumor positive sentinel nodes and did not contribute to the analysis of SN sensitivity [35; 36]. One study was excluded based on insufficient data to construct a 2 × 2 contingency table [37].

Ultimately, 20 studies concerning SN were included in this review to assess the sensitivity [5;7;11;36;38-53] and 23 to assess the SN detection rate [5;7;11;27;34-36;38-52;54] comprising a total of 842 patients (see table 3). The articles were divided in three groups; a. combined technique (12 articles), b. colloid only (5 articles), and c. blue dye only (4 articles). Two studies used 2 different techniques

Table 2. Quality assessment of included studies

Internal Validity							**External Validity**								
Study	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Barranger	2004	+	+	-	+	+	83%	+	+	-	+	+	+	+	+
Chung	2003	+	+	-	+	+	100%	+	-	-	+	+	+	+	+
Rob	2005	+	+	-	+	+	100%	+	+	+	+	+	+	+	+
Malur	2001	+	-	-	+	+	NM	+	+	+	-	+	+	+	-
Martinez	2004	+	+	-	+	+	100%	+	-	+	+	+	+	+	+
Pijpers	2004	+	-	-	+	+	100%	+	-	-	-	+	+	+	+
Rhim	2002	+	+	-	+	-	NM	-	-	-	+	-	+	+	-
Roca	2005	+	+	-	+	+	100%	+	+	+	+	+	+	+	-
Hubalewska	2003	+	-	-	+	+	100%	-	+	-	-	+	+	+	-
Lambaudie	2003	+	-	-	+	+	100%	+	-	-	-	+	+	+	+
Levenback	2002	+	-	-	+	+	100%	+	-	-	-	+	+	+	+
Niikura	2004	+	+	-	+	+	100%	+	-	-	+	+	+	+	+
Gil-Moreno	2005	+	-	-	-	+	100%	+	+	+	-	+	+	+	-
Silva	2005	+	+	-	+	+	100%	+	+	+	+	+	+	+	+
Lantsch	2001	+	+	-	+	+	100%	+	-	-	+	+	+	+	+
Li Bin	2004	+	+	-	-	+	100%	+	-	-	+	+	+	+	+
Van Dam	2003	+	+	-	+	+	88%	+	+	-	+	+	+	+	+
Lin	2005	+	+	-	+	+	100%	+	+	+	+	+	+	+	-
Angioli	2005	+	+	-	+	+	100%	+	+	+	+	+	+	+	+
Marchiole	2004	+	+	-	+	+	100%	+	+	-	+	-	+	NRTU	-
O'Boyle	2000	+	+	-	+	+	100%	+	-	-	+	+	+	NRTU	+
Di Stefano	2005	+	+	-	+	+	100%	+	+	+	+	+	+	NRTU	+
Echt	1999	+	+	-	-	+	100%	-	+	-	+	+	+	NRTU	+

NM= not mentioned (only 'early stage' is mentioned)NRTU= no radioactive tracer was used

for SN detection; the patients from these studies were divided in the combined technique group [36; 49] in the ^{99m}Tc colloid group [36] or the blue dye group [49].

Methodological qualitative analysis

There were 22 prospective studies. Inclusion criteria were described in 13 studies, and exclusion criteria in 9 studies. Sixteen studies included a consecutive patient population (see also table 2). The amount of injected blue dye varied from 0.2 ml. [54] to 4ml. [46]. The amount of activity (in MBq) of ^{99m}Tc varied from 10-20 MBq [48] to 228MBq [47] (Table 3). In all studies using a radioactive tracer a preoperative scintigraphy was performed. In 14/19 studies the 4-quadrant method was used.

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Table 3. Technique and tracer used

Study	Included patients	Tracer used	Technique used	Scinti-graphy	Histopathology	Method of surgery to obtain (Sentinel) nodes
Barranger (2004)	36	Patent blue dye ^{99m}Tc sulfur colloid	1 ml 4 quadrant, 80 MBq	+	3 mm interval, HE, IHC only on SN	Laparoscopy
Yong An Chung (2003)	26	Isosulfan blue dye ^{99m}Tc sulfur colloid	0.2 ml 4 quadrant, 60-100 MBq	+	Frozen biopsy, standard HE technique	Laparotomy
Rob (2005)	183	Patent blue dye ^{99m}Tc colloid	2 ml 4 quadrant, 20 MBq	+	Frozen section, 40 µm intervals, HE, IHC only on SN	39 laparoscopy 144 laparotomy
Malur (2001)	50	Blue dye ^{99m}Tc Albu-res	Not mentioned 4 quadrant, 50 MBq	+	HE staining	45 laparoscopy 5 laparotomy
Martinez (2004)	25	Isosulfan blue dye ^{99m}Tc human serum albumin	2-4 ml 20 MBq	+	0.2 mm interval, HE, IHC only on SN	7 laparoscopy 18 laparotomy
Pijpers (2004)	34	Patent blue dye ^{99m}Tc colloid	2-4 ml 4 quadrant, 228 MBq	+	Frozen section, 250 µm intervals, HE, IHC only on SN	34 laparoscopy
Rhim (2002)	26	Isosulfan blue dye ^{99m}Tc colloid	Not mentioned 2-3 depot 10-20 MBq	+	3 sections, HE	26 laparotomy
Roca (2005)	40	Isosulfan blue dye ^{99m}Tc colloid	2-4 ml 4 quadrant 74 MBq	+	0.2 mm sections, HE, IHC on all nodes	12 laparoscopy 28 laparotomy
Hubalewska (2003)	37	Patent blue dye ^{99m}Tc colloid	4 ml 4 quadrant, 100MBq	+	HE, IHC only on SN	37 laparotomy
Lambaudie (2003)	12	Patent blue dye ^{99m}Tc sulfur colloid	4 ml 4 quadrant, 74 Mbq	+	Frozen section, IHC only on SN	12 laparoscopy
Levenback (2002)	39	Isosulfan blue dye ^{99m}Tc colloid	4 ml 4 quadrant, 1-1.5 ml	+	Serial sectioning, HE, IHC only on SN	39 laparotomy
Niikura (2004)	20	Patent blue dye ^{99m}Tc phytate	4 ml 4 quadrant, 38-70 MBq	+	At least one section, HE IHC on all nodes	20 laparotomy
Gil-Moreno (2005)	12	Isosulfan blue dye ^{99m}Tc colloid	2-4 ml 4 quadrant, 40 MBq	+	0.2 mm sections, HE, IHC only on SN	12 laparoscopy
Silva (2005)	56	^{99m}Tc phytate	4 quadrant 55-74 MBq	+	2-3 mm intervals, HE, IHC only on SN	56 laparotomy
Lantsch (2001)	14	^{99m}Tc colloid	1 depot, 60-111 MBq	+	Serial sections, HE, IHC only on SN	14 laparotomy

Li Bin (2004)	28	^{99m}Tc dextran	2 location, 37 Mbq	+	ND	28 laparotomy
Van Dam (2003)	25	^{99m}Tc colloid	2 quadrant, 60 MBq	+	5 mm sections, HE, IHC only on SN	2 laparoscopy 23 laparotomy
Lin (2005)	30	^{99m}Tc colloid	4 quadrant, 202 Mbq	+	250 µm intervals, HE, IHC only on SN	30 laparotomy
Angioli (2005)	37	^{99m}Tc colloid	4 quadrant, 40-80 MBq	+	Serial sectioning, HE, IHC only on SN	37 laparoscopy
Marchiole (2004)	29	Patent blue dye	4 ml, 4 quadrant	-	Frozen sectioning, 3 adjacent slides sectioned at 200 µm intervals, HE, IHC on all nodes	29 laparoscopy
O'Boyle (2000)	20	Isosulfan blue dye	4 ml, 4 quadrant	-	ND	20 laparotomy
Di Stefano (2005)	50	Methylene blue dye	2 ml, 4 quadrant	-	200 µm serial step sections, HE, IHC only on SN	50 laparotomy
Echt (1999)	13	Lymphazurin dye	2 ml, 4 quadrant	-	ND	13 laparotomy

ND = no description
HE = hematoxylin and eosin staining
IHC = immunohistochemestry

All "blue dye only" studies (4) used the 4-quadrant method. Of the total of 842 patients, 265 (31.5%) underwent a laparoscopic procedure for lymph node (including SN) dissection. A node was considered sentinel in all studies when being blue, hot (audible gamma-probe signals of at least 10-fold above background levels, mentioned in all studies) or both. Two out of twenty-three studies failed to describe the histopathology technique how to detect lymph node metastases. All others used at least HE staining on all nodes. Of these, 6/23 also performed a frozen section on the SN. In most studies (16/23) an IHC staining was performed on the SN when the HE result was negative (70%). All others used HE staining only. Sectioning of the (sentinel) nodes was not uniformly performed. Multiple sectioning was mentioned in 11 out of 23 studies (48%). Of the 23 studies, 8 (35%) did not meet all internal validity criteria, as expected no author described a blinded test result for histopathology. However, in terms of the external validity criteria, the publications showed more heterogeneity (table 1 and 2).

Quantitative analysis (meta-analysis)

The sensitivity to detect lymph node metastases for all studies (two were excluded, n=21) was 89% (95% C.I.: 83-94%), with only a limited heterogeneity (chi-square 29.7, degrees of freedom-df-=20, p=0.075) Subgroup analysis for the three detection techniques revealed a homogeneous distribution if ^{99m}Tc only or the combined detection technique were used (chi-squared 9.2, df=11, p=0.60 for ^{99m}Tc colloid & blue dye and chi-square 5.3,df=4,p=0.26 for 99mTc alone). The results of the studies using blue dye were heterogeneous (chi-square 11.7, df=3, p=0.0085). ^{99m}Tc used alone or in a combination yielded a pooled sensitivity of 92% (see also figure 2). The pooled sensitivity for the blue dye detection was the lowest of the three detection techniques: 81% (67-84%, 95%CI), see figure 1. However, this pooled sensitivity of 81% was not significantly lower than either two other techniques (versus combined detection: Z=1.37; p=0.17 and versus ^{99m}Tc alone: Z=1.25, p=0.21).

For studies using ^{99m}Tc without blue dye the pooled SN detection rate was 88% (83 – 92%, 95% CI), and the data were heterogeneous (chi-squared = 22.81, d.f. = 6, p = 0.001). Finally, studies using only blue dye for detection of sentinel nodes in cervical cancer had a pooled SN detection rate of 84% (95% C.I.: 79 – 89%), and the data of these studies showed significant heterogeneity too (chi-squared = 23.83, d.f. = 4, p = 0.000). The SN detection rate was not significantly different for studies using 99mTc alone or blue dye alone (Z=1.14, p=0.25). The combined blue dye/^{99m}Tc technique had a significantly higher SN detection rate compared both to ^{99m}Tc alone (95-99% (95% CI), Z=3.13,p=0.0018) and blue dye alone (Z=3.92, p=0.00009), and studies showed homogeneous results (chi-squared 18.0, df=12, p=0.12).

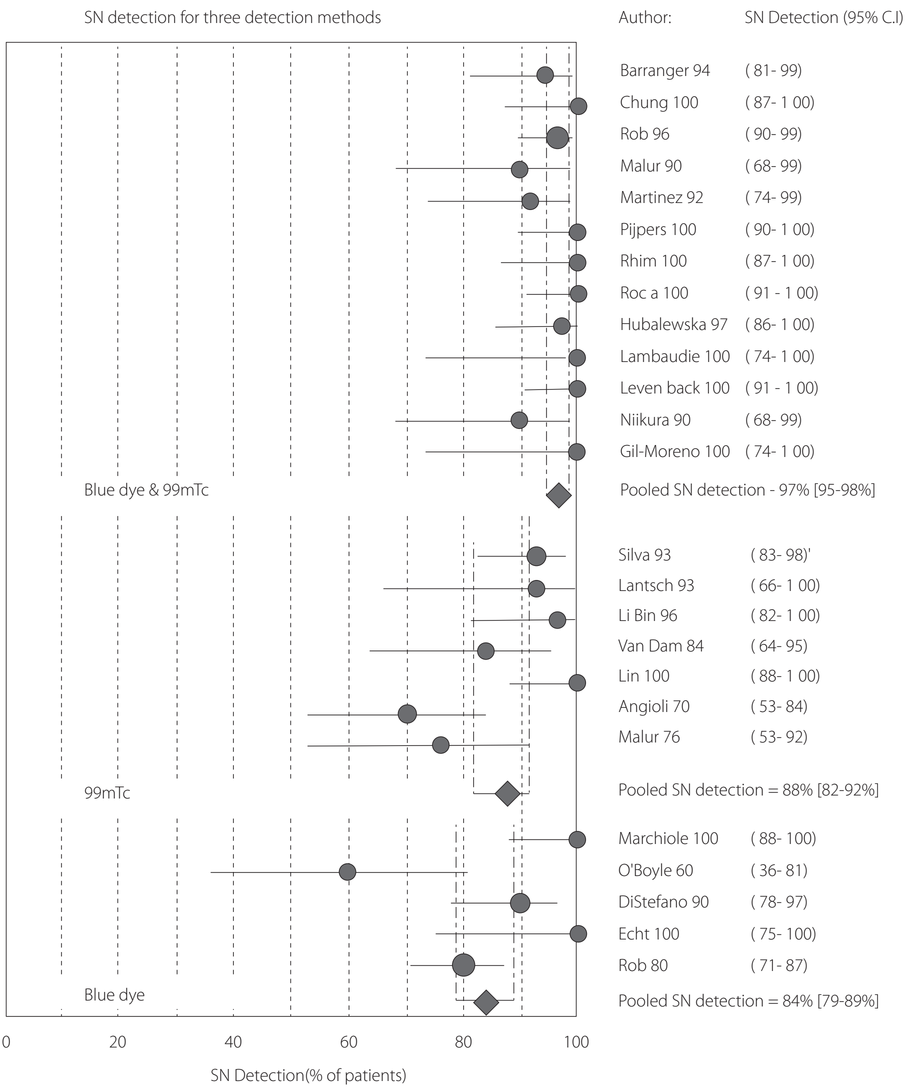

Figure 1: SN detection rate SN detection rates and 95% confidence intervals of individual studies concerning a SN procedure with a combined ^{99m}Tc -colloid & blue dye -, ^{99m}Tc -colloid or blue dye detection technique. Points represent individual study values, bars represent 95% confidence interval, and squares represent pooled values.

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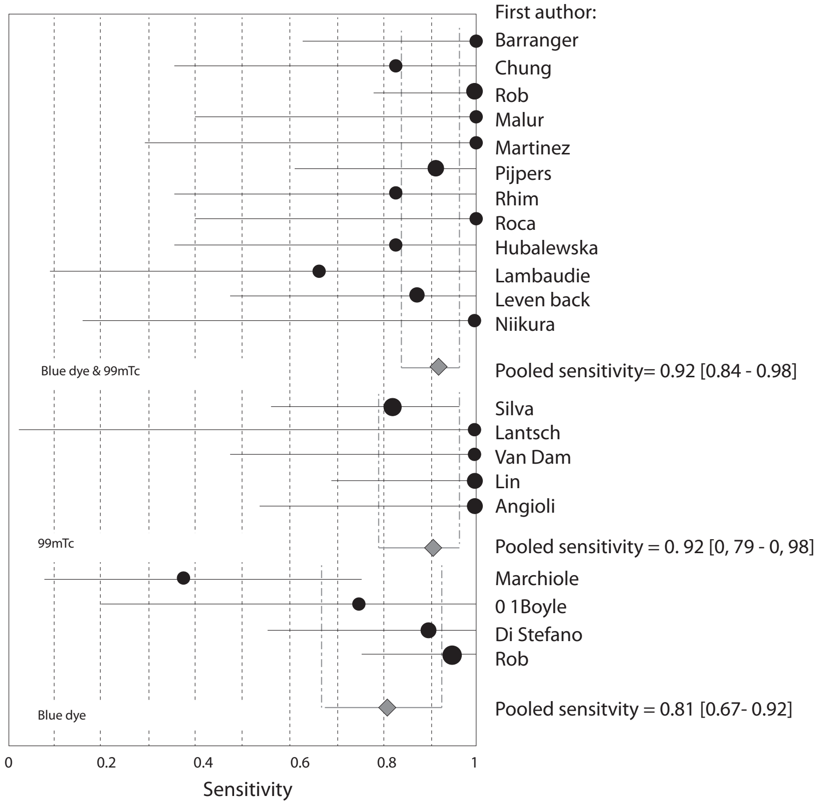

Figure 2: SN sensitivity Sensitivities and 95% confidence intervals of individual studies concerning the diagnostic accuracy of SN procedure with a combined ^{99m}Tc -colloid & blue dye -, ^{99m}Tc -colloid or blue dye detection technique. Points represent individual study values, bars represent 95% confidence interval, and squares represent pooled values.

Discussion

The aim of this systematic review is to summarize the available evidence for and to obtain valid and precise summary estimates of the diagnostic performance of the (laparoscopic) sentinel node technique for detecting lymph node metastasis in early cervical cancer.

The combined technique of ^{99m}Tc *and* blue dye yields the best results, with a pooled sensitivity of 92% and the highest SN detection rate of 97%. Technetium (^{99m}Tc) alone has a similar sensitivity of 92% but a 9% lower SN detection rate of 88%. SN detection with blue dye alone had the lowest SN detection rate of 84%. Furthermore the sensitivity was only 81%. Hence, the combined technique is the most successful technique with regard to both sensitivity and SN detection rate.

Detection rate

The SN detection rate in cervical cancer for the combined technique is comparable to the detection rate in cutaneous melanoma (95% vs. 98%) [55], and breast cancer (94-98%) [56]. We find little evidence in this review that the use of blue dye alone would suffice because of the lower detection rate, resulting in more failures of the procedure. Lacking the possibility to make a preoperative scintigraphy, blue dye is also less suited to detect extrapelvic sites such as the paraaortic region. The variation of SN detection with blue dye alone is also relatively high with two studies [27; 43] reporting SN detection rates of 100% and one study with a SN detection rate of only 60%. It is unlikely that a low amount of blue dye or low number of injections explains the relative low SN detection rate in this particular study since it used a 4-quadrant injection technique with a total amount of 4 ml. of blue dye [46]. In contrast, a study reporting a 100% SN detection rate with blue dye alone used 2ml. amount of blue dye and a single depot injection [27].

Most studies reported the use of a four-quadrant injection method and rarely at fewer sites. Most studies did not mention whether injection was done intra- or subepithelially, although this could theoretically make a difference, as could the type of blue used (lymphazurin, patent or methylene blue). However, with only 5 studies using blue dye alone for detection of SN we did not have enough data to evaluate the effect of the three different types of blue.

When using a radionuclide alone the detection rate is 88%. This seems to offer no advantage compared to the use of blue. Similar to the studies using blue dye alone the studies using ^{99m}Tc alone showed a significant variation. Sentinel node detection varied from 70% to 100%. The 7 studies using ^{99m}Tc alone used different amounts of ^{99m}Tc, varying from from 40 to 220MBq. Furthermore, not all studies used a four quadrant method and at least three different colloids were used. All these technical differences may have contributed to the variation we found in SN detection rates in studies using ^{99m}Tc alone. This variation of techniques also illustrates the need for standardization of the SN detection technique.

Adding blue dye to ^{99m}Tc resulted in a detection rate of 97%. The studies using the combined technique showed no significant variation in the detection rate. With this technique 13 study groups reached SN detection rates of more than 90%. The benefits of both techniques seem to add up: the use of preoperative scintigraphy to make an assessment of the localisation of the nodes especially at extrapelvic sites, combined with the intraoperative identification of lymph vessels with blue dye, and the nodes themselves by both the radionuclide and blue. Hence, the combined technique is a reliable way to detect SN.

Sensitivity

Sensitivity estimates are lowest for blue dye alone, with a pooled value of 81%. Using a radionuclide has a higher sensitivity of 92%, which is the same as with the combined technique. The sensitivity is comparable to SN biopsy in breast cancer (sensitivity 91.2%) [57]. Compared to the sensitivity of CT or MRI (43% and 60% for lymph node involvement [22], the sentinel node procedure is a more accurate way to detect tumor positive lymph nodes in cervical cancer.

One article [43] had a lower sensitivity (37,5%) and stated that Sentinel lymph node biopsy is *not* an accurate way to predict lymph node status, but we think this may be due to the fact that only blue dye was used, and not the combined technique in 27 of the 29 patients.

A factor, which should be taken into account, is the simultaneous introduction of more accurate techniques to detect tumor cells in the sentinel nodes. With the use of immunohistochemistry (IHC) it is now possible to detect micrometastases which previously remained undetected [58] and thus a more precise estimate of nodal status can be made. As recently stated by Gimbergues [59], in breast cancer serial sectioning detects 9%, IHC up to 25% and RT-PCR up to 30% of previously undetected micrometastases compared to HE staining. Theoretically this could give an overestimation of the sensitivity (in terms of detecting positive lymph nodes) of the SN procedure, because the non-SN will only undergo an HE staining. As stated by Van Trappen, the presence of micrometastases, which are often undetected by standard staining methods, could be a prognostic factor of metastatic recurrence. The detection of these micrometastases by means of a sentinel node may select patients for alternative treatment, although it remains to be seen whether chemo-radiation will improve survival in these patients.

The cervix has a complex lymphatic drainage due to its midline position, but in a fairly predictive manner as Leveuf and Godard stated in 1923 [60]. In this study however newborns were used, with a single dose of "preussian blue" in turpentine and only in two cases an adult with cervical carcinoma was examined. Still, they managed to describe what they called "the main pathways" of the nodal system related to the cervix, and the existence of "the interrupting nodes", most probably constituting what we nowadays know as the sentinel nodes. Referring to this article Plante, Dargent and Silva stated that a satisfactory SN detection is one with

SN on both sides, and SN status on one side does not predict the SN status of the other side [37; 51; 61]. Unfortunately, only 15/21 articles mentioned bilateral versus unilateral SN detection, or side of dissection. At this point, when in case of a (tumor) negative sentinel lymph node a complete lymphadenectomy is performed, the clinical relevance is yet unclear. Only when in the future one would completely rely on a single (or bilateral) lymph node to determine if the patient will be offered chemoradiation or a radical hysterectomy *without* a complete lymphadenectomy, this could become very important, and a full lymphadenectomy should remain to be performed at the side that does not come up.

The literature shows a large variation of techniques used for SN detection. In our opinion, there is a need for standardization of the SN detection technique, which could include the use of the four-quadrant method, a standard amount of blue (4 ml.) and ^{99m}Tc (at least 100MBq) and a standardisation of the (laparoscopic) surgery method.

At present, the combination of a radionuclide and blue seems to offer the best method to detect a SN and thus metastases if present in a sufficient number of cases and may therefore be used to select node positive patients who will require chemo-radiation. Time seems ripe to embark on a clinical study evaluating the safety and effectiveness of a SN procedure alone without a full lymphadenectomy in a lymph node negative patient.

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Open vs laparoscopic pelvic lymph node dissection in early stage cervical cancer: no difference in surgical or disease outcome.

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Abstract

Objective: To investigate in a retrospective study the effect of laparoscopic surgery introduced in our centre in 1994 as part of the standard treatment of early stage cervical cancer, on surgical and disease outcome.

Patients and methods: A total of 169 women with cervical carcinoma stage IB1 (N=150) or IB2 (N=19) were included in the study. Seventy-six patients who underwent laparoscopic pelvic lymph node dissection (LPLND), followed either by open radical hysterectomy (N=63) or, in case of positive lymph nodes, by primary chemoradiation (N=13), were compared with an historic cohort of 93 patients who underwent a fully open, traditional Wertheim-Meigs procedure (WM). Recorded patients' clinical characteristics included age, FIGO stage, histology, differentiation grade, tumor diameter, lymph node status, and adjuvant therapy. Operation time, lymph node yield, intraoperative, early and late complications, site of recurrences, and disease free and overall survival were analyzed and compared between groups.

Results: Clinical characteristics did not differ between groups. Duration of total surgery time was longer in the patients with LPLND followed by open radical hysterectomy than in the WM group ($P < 0.001$). In the patients with negative lymph nodes (N=129), the number of resected nodes was higher ($P = 0.002$) in the LPLND (median 26 nodes, range 8-55) than in the WM group (median 21 nodes, range 7-50). In the patients with positive lymph nodes (N=40), no significant difference in the number of resected lymph nodes between the two groups ($P = 0.904$) was found. Intraoperative, early and late complications did not differ between the two surgical procedures. The number of loco-regional recurrences, but not of distant metastases, was significantly higher ($P = 0.018$) in the WM group compared to the LPLND group. No difference in disease-free (DFS) or disease-specific survival (DSS) was found between the LPLND and WM group, neither with or without adjuvant or primary (chemo)radiation. A benefit in DFS ($P = 0.044$), but not in DSS ($P = 0.070$), was found in the LPLND compared to the WM group, in those patients that received adjuvant therapy or primary chemoradiation.

Conclusion: the introduction of a laparoscopic procedure in the surgical staging and treatment of cervical cancer patients did not have a detrimental effect on surgical or disease outcome, and can be safely applied to the treatment of early stage cervical cancer.

Introduction

The choice of treatment for early stage cervical cancer depends on the presence or absence of lymph node metastases, which is, together with tumor size, a dominant prognostic factor for disease outcome [1,2,3]. The recommended treatment for stage IB-IIA cervical cancer with clinically negative lymph nodes is a radical hysterectomy and pelvic lymph node dissection. If the lymph nodes are tumor positive, patients are offered (chemo)radiation [4]. Laparoscopic lymph node dissection (LPLND) instead of open surgery is increasingly being used as staging procedure or as integral part of radical surgery for cervical cancer. An adequate number of lymph nodes can be removed, and complications are minimal [5,6,7].
Despite its widespread use, the advantage and safety of laparoscopic over open pelvic lymph node dissection is still under discussion, mainly because of concerns about the oncologic outcome. Cases of port-site metastases (PSM) after laparoscopic lymph node staging of cervical cancer have been reported [8,9], a phenomenon also seen after laparoscopic surgery for colorectal [10] and ovarian cancer [11,12]. Also, the occurrence of metastases could be influenced both in time and site by the use of laparoscopy [13,14]. The pneumoperitoneum in itself seems to have an effect on local immune reactions, facilitating the growth and hematogenous spread of tumor cells [15,16]. On the other hand, animal studies [17] have shown laparotomy to induce more tumor growth than laparoscopy, probably due to a better preservation of immune function in case of laparoscopy.
Recent studies show that a laparoscopic radical hysterectomy with laparoscopic lymph node dissection leads to less blood loss, less infections, equal margins, shorter hospital stay but longer operation time [18,19]. The aim of this study is to investigate the effect of laparoscopy on surgical and disease outcome in early stage cervical cancer. To this end LPLND is compared with the traditional open lymph node dissection. In our centre, laparoscopic lymph node dissection was first introduced in 1994. The LPLND group includes patients treated after this period. Radical hysterectomy in either case was still performed by open surgery and chemoradiation was given in case of extra-cervical extension of the tumor. A sentinel node was not part of standard treatment for the traditional open lymph node dissection group, but was performed in the majority of cases in the LPLND group. Comparison included lymph node yield, surgical, early and late complications, and number and localization of recurrences, as well as disease outcome.

Materials and methods

Study population

One hundred and seventy nine women with FIGO stage IB1 or IB2 cervical cancer treated surgically at the department of Obstetrics and Gynecology of the VU University medical centre between January 1988 and December 2005 were included in the study. Patients operated from 1988-1994 all underwent a classic open radical hysterectomy according to Wertheim-Meigs (WM), from 1994-2002 both techniques (laparoscopic or open lymphadenectomy) were practiced and from 2003-2005 except for one case only a laparoscopic lymphadenectomy (level 2 according to Querleu and Morrow) was performed. Radical hysterectomy was always performed according to Querleu and Morrow classification C2, with the inclusion of a partial nerve-sparing technique (C1) from 2003 onwards [20] Patients who underwent a radical vaginal trachelectomy were excluded from the study.

All clinical charts were reviewed for clinical and pathological characteristics. Ten patients were excluded from the study for the following reasons: in one open case the procedure was combined with a caesarean section, five patients underwent only a lymph node biopsy, and in four cases the laparoscopy was converted to laparotomy because of anesthetic or technical problems. Two groups were defined according to the use of laparoscopy as part of the surgical treatment: 1) women who underwent LPLND followed by radical hysterectomy performed in one or in separate sessions (N=63) or, in case of positive lymph nodes, chemoradiation (N=13) (LPLND group), and 2) women who underwent a fully open pelvic lymphadenectomy and radical hysterectomy according to Wertheim-Meigs (n=93) (WM group).

Data was retrieved on age, FIGO stage, histology, differentiation grade, tumor diameter, number of excised lymph nodes, node status, operation time, surgical, early and late complications, and disease outcome. Patients were followed for at least five years. Data on patient outcome was reviewed until December 2009, and was available for all but four patients. One patient was lost to follow up in the first, two in the second, and one in the third year after treatment. As at the time there was no evidence of disease, these data were treated as censored observations. The principal events analyzed were recurrence and death. Disease free survival (DFS) was defined as the time elapsed between the start of primary treatment and the first reappearance of cervical cancer at any site, or the date of the last visit for patients with no evidence of disease. Site of recurrence was recorded. Disease-specific survival (DSS) was defined as the time elapsed between primary treatment and death from cervical cancer, or the date of the last visit for all other patients. Four patients died of causes other than cervical cancer. They had no evidence of disease, and were treated as censored observations.

Procedures followed were in accordance with the Helsinki declaration of 1975, as revised in 1983, and in accordance with the guidelines for research from our institute.

As this study constituted a retrospective evaluation of usual clinical practice no review board approval was required.

Statistical methods

Statistical analysis was performed using SPSS software (Version 16.0, SPSS Inc, Chicago, IL.). The distribution in contingency tables of clinical and pathological characteristics between groups was analyzed with the Pearson χ^2 test or, when the sample size was small, the Fisher's exact test (2-sided). Results in the different patient groups were analyzed using the T-test or the Mann-Whitney *U/* Wilcoxon rank sum W Test, as appropriate. Univariate and multivariate analyses of DFS and DSS were performed in the total population using the Cox proportional hazards regression model [21]. The model included the following clinical and pathologic features as potential predictors: age, FIGO stage (IB1 or IB2), lymph node involvement (negative or positive), histology (squamous cell carcinoma, adenocarcinoma, or mixed), differentiation grade (I, II or III), tumor diameter (≤4cm or >4cm), and pelvic lymph node dissection procedure (laparoscopic or open). The probability of DFS and DSS in relation to the pelvic lymph node dissection procedure was analyzed using the Kaplan-Meier method [22], and univariate comparisons between subgroups were made using a two-tailed log-rank test; *P*-values equal or smaller than 0.05 were considered statistically significant.

Results

One hundred and sixty nine women were included in the study. Table 1 lists the clinicopathological characteristics of the patients and their primary treatment. Distribution of demographic and clinicopathological characteristics (age, FIGO stage, histology, grade, tumor diameter and lymph node status) did not differ significantly between the patients in the LPLND (N=76) or WM group (N=93).

LPLND followed by radical hysterectomy was performed in one session in 37 patients, and in two sessions (one week apart) in 26 patients. A sentinel node procedure was done as part of the laparoscopy in 43 patients. A total of eight patients received adjuvant therapy because of either the presence of lymph node metastases (N=6), parametrial invasion (N=1), or tumor extension to the vaginal fornix (N=1). One patient with a few isolated tumor cells in one lymph node did not receive adjuvant therapy. Thirteen patients received primary chemoradiation because of positive lymph nodes found at laparoscopic pelvic lymph node dissection.

Ninety-three patients underwent a traditional WM procedure, followed by adjuvant radiotherapy or chemoradiation in 24 cases. Eighteen patients received adjuvant therapy because of positive lymph nodes. Additionally, six patients with negative lymph nodes received adjuvant therapy because of either insufficient resection margins (N=4), bulky disease and an undifferentiated tumor (N=1), or the presence of lymphovascular space invasion distant from the tumor (N=1). Two lymph node positive patients that had a micrometastasis in only one lymph node did not receive adjuvant therapy.

The number of excised lymph nodes (Table 2) was higher in the LPLND than in the WM group ($P = 0.011$). Notably, the number of lymph nodes obtained in either of the two surgical procedures was higher in the group of patients with negative lymph nodes ($P = 0.002$) and LPLND, but did not differ significantly between procedures in the group of patients with positive lymph nodes ($P = 0.904$).

Table 2. Number of excised lymph nodes according to lymph node status in the laparoscopic (LPLND) and open (WM) lymph node dissection group

	Total population			**LN negative**			**LN positive**		
	N	**Median (range)**	***P****	**N**	**Median (range)**	***P****	**N**	**Median (range)**	***P****
LPLND	76	25.5 (8-55)	0.011	56	26 (8-55)	0.002	20	22 (8-46)	0.904
WM	93	22 (7-56)		73	21 (7-50)		20	25 (7-56)	

*Mann-Whitney *U* test

The total duration of surgery was significantly longer ($P < 0.001$) for the LPLND followed by open radical hysterectomy group (mean 400 min, SD 78.8) compared to the WM group (mean 323.7 min, SD 68.1). Within the LPLND group, no significant difference in total operation time ($P = 0.234$) was found between the groups undergoing open radical hysterectomy in one session (mean 410 min, SD 77.7) or in two separate sessions (mean 385.7 min, SD 79.8).

Surgical, early and late complications did not differ significantly between the LPLND and WM group. For the evaluation of late complications, patients who received adjuvant (chemo-)radiation were excluded from the analysis. Three, seven and one patients in the LPLND group, and five, five, and one patients in the WM group had

Table 1. Clinicopathological characteristic of the study population

	Laparoscopic lymph node dissection (LPLND)			Traditional Wertheim-Meigs (WM)	Total population
	Radical hysterectomy*	Chemoradiation	Total LPLND		
N (%)	63 (37.3)	13 (7.7)	76 (45.0)	93 (55.0)	169 (100)
Age (years), median (range)	41 (22-73)	37 (29-72)	41 (22-73)	44 (25-89)	41 (22-89)
FIGO stage, N (%)					
IB1	56 (88.9)	12 (92.3)	68 (89.5)	82 (88.2)	150 (88.8)
IB2	7 (11.1)	1 (7.7)	8 (10.5)	11 (11.8)	19 (11.2)
Histology, N (%)					
Squamous cell carcinoma	47 (74.6)	9 (69.2)	56 (73.7)	67 (72.0)	123 (72.8)
Adenocarcinoma	14 (22.2)	4 (30.8)	18 (23.7)	22 (23.7)	40 (23.7)
Mixed	2 (3.2)	0 (0)	2 (2.6)	4 (4.3)	6 (3.5)
Differentiation grade, N (%)					
I	5 (7.9)	2 (15.4)	7 (9.2)	3 (3.2)	10 (5.9)
II	28 (44.4)	7 (53.8)	35 (46.0)	35 (37.6)	70 (41.4)
III	30 (47.6)	4 (30.8)	34 (44.7)	55 (59.1)	89 (52.7)
Tumor diameter, N (%)[§]					
≤4cm	49 (80.3)	9 (90)	58 (81.7)	75 (85.2)	133 (83.6)
>4cm	12 (19.7)	1 (10)	13 (18.3)	13 (14.8)	26 (16.4)
Node status, N (%)					
Negative	56 (88.9)	0 (0)	56 (73.7)	73 (78.5)	129 (76.3)
Positive	7 (11.1)	13 (100)	20 (26.3)	20 (21.5)	40 (23.6)
Adjuvant therapy, N (%)					
Radiotherapy	6 (9.5)	-	-	18 (19.4)	24 (14.2)
Chemoradiation	2 (3.2)			6 (6.5)	8 (4.7)
Recurrences, N (%)	7 (11.1)	2 (15.4)	9 (11.8)	19 (20.4).	28 (16.6)
Deaths from cervical cancer[¶], N (%)	6 (9.5)	2 (15.4)	8 (10.5)	16 (17.2)	24 (14.2)
Disease free survival (years), median (range)	4.9 (0.3 – 12.3)	5.1 (0.95 -8.2)	4.9 (0.3-12.3)	5.2 (0.4 – 16.9)	5.0 (0.3 -16.9)
Disease-specific survival (years), median (range)	4.9 (1.0 – 12.3)	5.2 (1.2 – 8.2)	5.0 (1.0-12.3)	5.3 (0.4 – 16.9)	5.4 (0.4 – 16.9)

*LPLND and radical hysterectomy in one session, N=37; in separate sessions, N=26.
[§]Information on tumor diameter was not available in 10 cases.
[¶]Four patients in the traditional Wertheim-Meigs group died of unrelated causes, with no evidence of cervical cancer recurrence at the time of death.

more than one surgical, early, and late complication, respectively. Results are summarized in Table 3.

Table 3. Summary of complications of laparoscopic (LPLND) or open lymph node dissection followed by radical hysterectomy (WM)

Complications*	**LPLND**	**WM**	***P***
	N=63	**N=93**	
Intraoperative	**N (%)**	**N (%)**	
None	40 (63.5)	65 (69.9)	0.487
Blood loss≥2500 mL	15 (23.8)	20 (21.5)	0.845
Bladder injury	3 (4.8)	1 (1.1)	0.304
Ureter injury	1 (1.6)	2 (2.2)	1.0
Bowel injury	0	1 (1.1)	1.0
Vascular injury	6 (9.5)	7 (7.5)	0.770
Corpus alienum (surgical instrument)	1 (1.6)	1 (1.1)	1.0
Early			
None	25 (39.7)	44 (47.3)	0.412
Ileus	1 (1.6)	0	0.404
Surgical wound dehiscense	0	1 (1.1)	1.0
Surgical wound infection/abcess	3 (4.8)	2 (2.2)	0.394
Infection (unspecified)	4 (6.3)	7 (7.5)	1.0
Urinary tract infection	5 (7.9)	7 (7.5)	1.0
Impaired micturition	30 (47.6)	35 (37.6)	0.248
Thromboembolism	0	1 (1.1)	1.0
Lymphocele	0	1 (1.1)	1.0
Lymphedema	2 (3.2)	1 (1.1)	0.566
Late (>3 months after surgery)[§]	**N=55**	**N=68**	
None	38 (69.1)	52 (76.5)	0.415
Bladder Disfunction	4 (7.3)	5 (7.4)	1.0
Rectal Disfunction	2 (3.6)	1 (1.5)	0.586
Fistula	4 (7.3)	4 (5.9)	0.730
Lymphedema	7 (12.7)	6 (8.8)	0.562
Hydronephrosis	3 (5.5)	1 (1.5)	0.324

* Data are incidence of complications and not number of patients, as some patients may have experienced more than one of the complications listed.
[§]Listed only for patients that did not receive adjuvant radiotherapy or chemoradiation.

Site of recurrence and disease outcome

Recurrences and deaths in the study population are listed in Table 1. In the LPLND group 11.8% of patients recurred, compared to 20.4% in the WM group. (*P* = 0.151). Eight (10.5%) and 16 (17.2%) patients died of cervical cancer in the LPLND and WM group, respectively (*P* = 0.270).

The number of loco-regional recurrences was significantly higher (*P* = 0.018) in the WM group compared to the LPLND group (Table 4). The site of distant metastases did not differ among the two groups (*P* = 0.470). No port-site metastases were observed.

Table 4. Site of first recurrence in the laparoscopic (LPLND) and open (WM) lymph node dissection study group.

	LPLND N=76	WM N=93	*P* value*
Locoregional – total	4	16	0.018
- vagina top	2	6	
- lymph nodes	2	9	
- bowel	0	1	
Distant – total	5	3	0.470
- liver	1	0	
- lung	2	3	
- supraclavicular lymph nodes	2	0	

*Fisher exact test

Cox regression analysis of DFS and DSS in relation to disease characteristics and pelvic lymph node dissection procedure was performed in the total population. In univariate analysis, only the tumor diameter (≤4cm or > 4cm), and the lymph node status (negative or positive), were significantly associated with DFS (P <0.001 and *P* = 0.003, respectively) and DSS (P <0.001 in both cases). Multivariate analysis identified tumor diameter and lymph node status as independent predictors for DFS and DSS.

Although the type of method of pelvic lymph node dissection (laparoscopic or open), was not significantly associated with DFS and DSS in univariate analysis (P = 0.201 and *P* = 0.344, respectively), it was significantly associated with DFS (*P* = 0.032) in multivariate analysis in favor of the laparoscopic procedure (Table 5).

Table 5. Multivariate analysis of disease characteristics and surgical procedure evaluated for an association with outcome of disease in the total population (N=169)

	DSS		DFS	
Factors	**HR (95% CI)**	***p* value**	**HR (95% CI)**	**p value**
LPLND *vs.* WM	1.86 (0.72 – 4.81	0.197	2.68 (1.09 – 6.62)	0.032
Tumor diameter ≤ 4cm *vs.* ≥ 4cm	4.85 (1.83 – 12.89)	0.002	7.69 (3.02 – 19.56)	<0.001
LN neg. *vs.* pos.	4.73 (1.89 – 11.86)	0.001	4.06 (1.69 – 9.77)	0.002

HR, hazard ratio

Kaplan Meier analysis, however, of DFS and DSS in the total population in relation to the type of pelvic lymph node dissection procedure (LPLND *vs.* WM) showed no significant differences between groups ($P = 0.201$ and $P = 0.344$, respectively). Furthermore, in those patients that did not receive adjuvant therapy (n = 124), no significant difference in disease outcome between the two groups was found (Fig.1A and B). In patients that received adjuvant therapy or primary chemoradiation, a marginal benefit for DFS (Fig.1C), was found in the LPLND group (85%, mean 7.16 yrs, 95% CI 6.12 – 8.20 yrs) compared to the WM group of patients. (54%, mean 10.06 yrs, 95% CI 6.93 – 13.19 yrs). No significant difference in DSS between the two groups was found (Fig.1D).

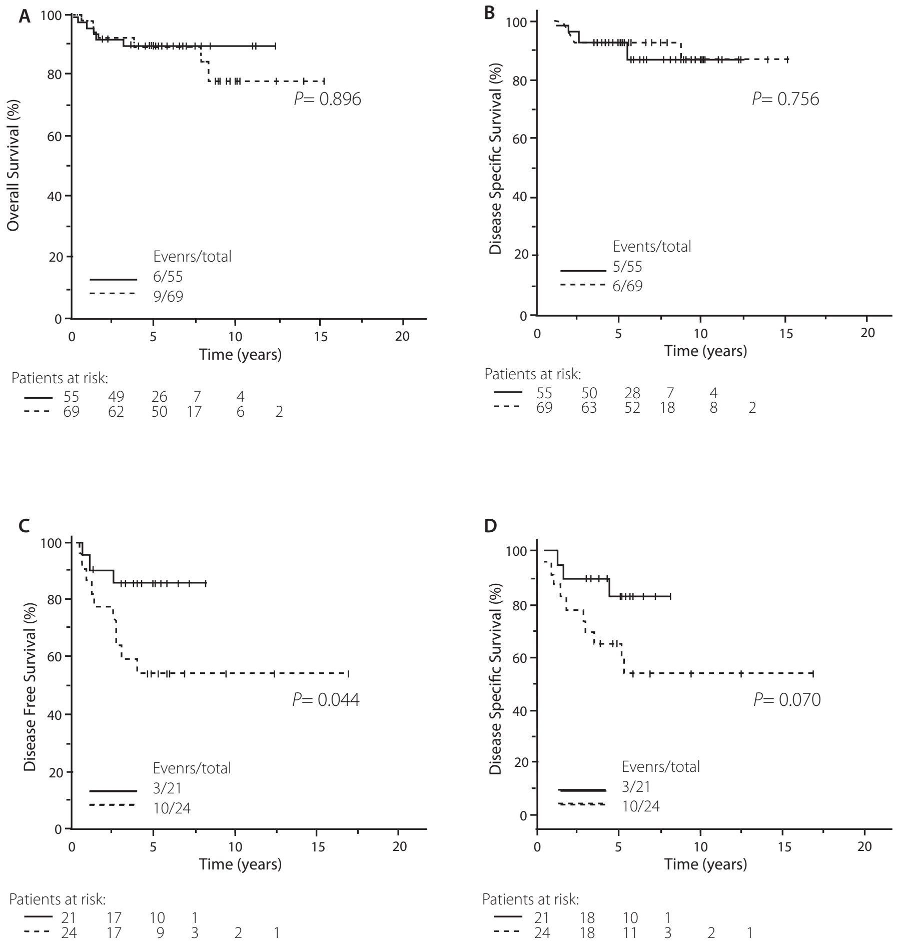

Figure 1 A-D Kaplan Meier graphs of DFS (A and C), and DSS (B and D) in relation to laparoscopic (LPLND) or open (WM) lymph node dissection in patients that received no adjuvant therapy (A and B), and in patients that received adjuvant therapy or primary chemoradiation (C and D). Solid line indicates LPLND; broken line, WM.

Discussion

The addition of a laparoscopic procedure (LPLND) in combination with open radical surgery did not alter the frequency of intra-operative, early and late complications, and neither did it influence the site of distant recurrences. However, lymph node yield tended to be higher in the laparoscopy group than in the WM group, and less loco-regional recurrences and a better DFS were seen after laparoscopy.

This study confirms that laparoscopic lymph node yield is at least as high as that obtained with laparotomy [24,25,26,27,28] It could be argued that the higher lymph node yield observed in our study with laparoscopy is a result of the procedure being performed in an era where we pay more attention to meticulous dissection, thus yielding more nodes. In case of positive lymph nodes, the number of excised lymph nodes did not differ significantly between groups This was anticipated, as in both groups when frozen sections showed nodal involvement, a less complete pelvic lymph node dissection was performed.

Recurrence rates in our study population (16.6%) are comparable with the 13 to 25% mentioned in the literature [29-31]. The pattern of recurrences observed in our study indicates no deleterious effect of laparoscopy in comparison to open lymph node dissection. There was no difference in the number and site of distant metastases between the two surgical approaches, but loco-regional recurrences occurred less frequently in the laparoscopy group. As a consequence of the NCI alert of 1999, a larger number of patients in the LPND group than in the historic WM group received chemoradiation (adjuvant or primary) instead of radiation alone (Table 1). This may have resulted in a better loco-regional disease control [32]. In this respect, in the Radiation Therapy Oncology Group (RTOG) 90-01 trial the number of loco-regional recurrences for high-risk cervical cancer was reduced by the addition of chemotherapy to radiation. [33].

In the group of patients that underwent radical hysterectomy and did not receive adjuvant therapy, DFS and DSS did not differ significantly between the two lymph node dissection procedures (Fig.1A and B), suggesting that laparoscopy has no deleterious effect on outcome of disease. Furthermore, a significant benefit in DFS ($P = 0.044$), but not in DSS ($P = 0.070$), was observed in patients that underwent LPLND compared to open lymphadenectomy, in the group of patients that received primary or adjuvant (chemo)radiation. This benefit in outcome of the LPLND group could again be a reflection of the addition of chemotherapy to radiation therapy, as chemoradiation next to reducing the risk of locoregional recurrences has a survival benefit over radiotherapy alone [34-38].

In most European countries it is common practice to avoid radical hysterectomy and treat patients with positive lymph nodes with primary chemoradiation. This is, however, not the case for all countries as NCCI guidelines do not recommend primary chemoradiation instead of radical hysterectomy followed by chemoradiation as standard treatment for patients with positive lymph nodes [4,23]. Laparoscopic lymph node assessment offers the possibility to omit radical hysterectomy in patients with positive lymph nodes that will subsequently receive chemoradiation, consequently avoiding the added morbidity of (unnecessary) radical hysterectomy, as well as the higher risk of radiation enteritis in case of open surgery plus chemoradiation [30].

Although the estimated incidence of PSM after laparoscopic surgery reported in the literature varies widely from 0-21% [13], according to Martinez and colleagues PSM is a rare complication in cervical cancer, with an incidence of only 0.43% [14]. No port-site metastases were observed in our study population.

The present study covers a period in which radical hysterectomy was not yet performed by laparoscopy, and thus this part of the procedure was done by laparotomy, even if LPLND had been performed. Furthermore, before the introduction of LPLND, no sentinel node procedure and standard frozen section of the lymph nodes was performed. In the WM group the necessity for adjuvant therapy by means of (chemo)radiation was therefore made after examination of all surgical specimens. The method of preference for cervical cancer surgery in our center today is a (robot assisted) laparoscopy, with the addition of a sentinel node procedure.

Although at the time of our study laparoscopy was only partly implemented in the surgical treatment of early stage cervical cancer, and study results may be limited due to a non-randomised setting comprising a limited number of patients coming from a single institution, our evaluation allows us to conclude that its introduction does not lead to adverse effects. This is important as minimal invasive techniques, such as laparoscopic or robotic assisted laparoscopic lymphadenectomy and radical hysterectomy, are increasingly being used in the treatment of cervical carcinoma. Today, with the introduction of laparoscopic radical surgery, laparoscopic lymph node dissection can be used as a staging procedure, where a decision for a minimal invasive therapy (i.e. a radical vaginal trachelectomy (RVT) or laparoscopic radical hysterectomy) can be made on the basis of both preoperative assessment and laparoscopic findings. As such, the laparoscopic approach does not seem to jeopardize the excellent results that have been obtained by open radical surgery used almost unchanged for over a century.

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6

Radical vaginal trachelectomy in the Netherlands

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Abstract

Objectives. Radical vaginal trachelectomy (RVT) offers the possibility to preserve fertility in young women with early stage cervical cancer. Here we describe the Dutch experience with this operation since its introduction in three centers in the Netherlands in February 2000.

Patients and Methods. A total of 67 RVT procedures combined with laparoscopic pelvic lymphadenectomy were carried out between February 2000 and July 2008 in women with cervical tumors up to 2 cm in diameter. Initial diagnostic procedures included 7 biopsies, 40 large-loop excisions of the transformation zone (LLETZ) and 20 conizations.

Results. After a median follow up of 60 months three recurrences and no disease related deaths have occurred. Three patients required adjuvant treatment due to positive resection margins and/or tumor extension up to the endocervix or vagina. No relation was found between tumor width or tumor depth of the diagnostic sample and residual tumor in the RVT specimen. Ten out of 19 conization specimens had tumor-positive resection margins; however, residual tumor was present in the RVT specimen in only half of these 10 cases. Thirty-one pregnancies were observed during follow up, of which two women were already pregnant at the time of the surgical treatment, and one patient was 30 weeks pregnant at close of study in January 2012. Twenty healthy babies were born with only one before the third trimester of pregnancy. Seven early (<14 weeks) miscarriages occurred, and 2 women delivered at 15 and 20 weeks gestational age, respectively. Additionally, 2 pregnancies were terminated for non-medical reasons.

Conclusions. RVT is a safe way to preserve fertility in young women with small stage I cervical carcinoma. The number of live births was comparable to that reported in the literature, and the procedure had favorable disease outcome, probably due to the strict criteria applied in the selection of patients. Conization instead of RVT seems insufficient at this point to guarantee adequate tumor-free resection margins.

Introduction

The effective use of cervical cancer screening programs has led to an increasing number of women diagnosed with cervical cancer at a younger age [1]. In the Netherlands, the peak incidence of cervical carcinoma lies between 30 and 50 years of age. One-third of the patients diagnosed with IA2-IB1 cervical cancer is under the age of 40 [2]. A number of these patients have not yet started or completed their family and wish to preserve fertility.
Radical hysterectomy as the standard treatment for early stage invasive cervical carcinoma eliminates the capacity of women to bear children. In order to preserve fertility new concepts have risen regarding function preservation using minimally invasive techniques in the surgical treatment of women diagnosed with early stage cervical cancer [3]. The most common novel surgical procedure is the radical vaginal trachelectomy (RVT) combined with pelvic lymph node dissection (PLND) as described by Dargent in 1994 [4]. Since then, more than 900 procedures have been published worldwide [3,5,6,7]. Recurrence rate is low (3.7%) as is the number of deaths (2%), and the obstetrical outcome is promising. A literature review of 256 pregnancies following RVT indicates that 40% of them will culminate with the birth of a healthy newborn at term [5].
RVT was introduced in the Netherlands in the year 2000 in 3 different university hospitals. The aim of the study is to describe the Dutch results with RVT over an eight-year period after its introduction.

Materials and Methods

Study population

Between February 2000 and July 2008 RVT was performed in 67 patients in three centres in the Netherlands, if patients met the following criteria: a strong wish to preserve fertility, ≤ 40 years of age, stage IA2 or IB1 cervical carcinoma with tumor-size (estimated by MRI, CT, examination under general anesthesia and/or diagnostic excision) not exceeding 2 cm at its largest diameter, and no suspicion of parametrial or lymph node metastases.
LVSI in the diagnostic specimen was not an exclusion criterion for the procedure. Sixty-five women met the inclusion criteria and were counseled as to their treatment options, and offered the choice between standard (radical hysterectomy according to Wertheim- Meigs) and fertility preserving treatment. Three women were included in the study that did not fulfill the inclusion criterion of desiring to preserve fertility but wished to preserve their uterus. Of the 64 remaining patients

who fulfilled inclusion criteria, two were already pregnant when surgery was performed.

Histological diagnosis was made by biopsy, large loop excision of the transformation zone (LLETZ) or conization.

Age, parity, histological type, grade, size (width and depth), and extension of the tumor, lymph vascular space involvement (LVSI), lymph node count, site and number of positive lymph nodes, operation room (OR) time, as well as blood loss, and intraoperative and postoperative complications were recorded. Postoperative complications recorded were bladder dysfunction such as retention or incontinence, urinary tract infection, fever, neuropathy and cervical stenosis.

Procedure

First, a pelvic lymph node dissection (PLND) by laparoscopy was performed, in 22/67 cases preceded by a sentinel node procedure. The pelvic lymphadenectomy was followed by a vaginal resection of the cervix including resection of the parametrial tissue and excision of a vaginal cuff. Multiple frozen sections of the upper portion of the resected specimen were performed. In case of a tumor-free endocervical margin less than 5 mm, a further resection of the cervix or a radical hysterectomy was performed. In case of satisfactory resection margins, a permanent cerclage was placed around the lower uterine segment. An intra-uterine catheter was left in situ for at least three days, with a maximum of two weeks. In case of positive lymph nodes or narrow (<5mm) resection margins not detected by frozen section subsequent hysterectomy was performed and/or the patient received postoperative (chemo-) radiation.

Follow up data for analysis were collected until January 2012. Follow-up (physical examination, cytology, MRI if indicated) consisted of three monthly visits in the first and second year, and every four- to six months in the third to fifth year. Median follow-up was 60 months (12 to 122 months). Two patients were lost to follow-up after 12 and 21 months; all other patients were followed for at least 31 months. Recurrences were recorded at the date of histological diagnosis. For those patients attempting to conceive the number and outcome of pregnancies were recorded.

Statistical methods

Statistical analysis was performed using SPSS software (Version 15.0, SPSS Inc, Chicago, IL.). Tumor width and depth and residual tumor in the RVT specimen were evaluated by the receiver-operating characteristic (ROC) method. The distribution of tumor width and depth above or below the cutoffs of 7 mm and 5 mm, respectively, was analyzed in contingency tables according to the presence of residual tumor in the RVT specimen with the Pearson $\chi 2$ test or, when the sample size was small (any one cell with expected count <5), the Fisher's exact test. Results with *p* values ≤0.05 were considered statistically significant.

Results

Table 1 describes the patient population and pathological variables. Median age was 31 years (range 23-41 years). Forty-two patients (63%) were nulliparous. Two patients were 9 weeks and 18 weeks pregnant at the time of diagnosis, two patients had a stage IA2 cervical carcinoma (3%), 65 (97%) had stage IB1 disease. Squamous carcinoma was present in 79%, adenocarcinoma in 18%, and adenosquamous and clear cell each in 1.5 % of cases. LVSI was present in 24% of cases. Median lymph node count was 17 (range 2-41) (Table 1).

Table 1. Clinicopathological characteristic of the patients with cervical cancer (N = 67)

Age in years, median (range)	**31 (23-41)**	
Characteristics	**N**	**%**
Parity		
0	42	63.0
1	17	25.0
2	6	9.0
3	2	3.0
Pap smear		
2 (borderline)		
3a (mild/ moderate dyskariosis)	1	1.5
3b (severe dyskariosis)	14	20.9
4 (carcinoma in situ)	21	31.3
5 (carcinoma)	25	37.3
Not known	2	3.0
	4	6.0
Method of diagnosis		
Biopsy	7	10.5
Large loop excision of the transformation zone	40	69.7
Conization	20	29.8
Stage, N (%)		
IA2	2	3.0
IB1	65	97.0
Histological type		
Squamous-cell carcinoma	53	79.0
Adenocarcinoma	12	18.0
Adenosquamous carcinoma	1	1.5
Clear-cell carcinoma	1	1.5
Histological grade		
I	7	10.5
II	32	47.8
III	20	29.8
Not known	8	11.9

Lymph vascular space invasion*		
Absent	49	73.0
Present	16	24.0
Number of lymph nodes resected, median (range)§	17 (2 – 41)	
Radiation or chemoradiation	3	4.5
Follow up interval in months, median (range)	60 (12 – 122)	

*Not reported in two cases
§IHC revealed isolated tumor cells (lesion diameter 69.7µm) in sentinel node.

Diagnosis was mostly made by excision (60% by LLETZ, 30% by conization) and only in 10% of cases through biopsy (Table 1). Median tumor size in the diagnostic specimen (Table 2) was 8 mm (range 2-21 mm), and median preoperative depth of invasion was 4 mm (range 2-21 mm). Information on the resection margins of the diagnostic specimen could be retrieved in 53 cases (Fig. 1).

Table 2. Tumor width and depth of tumor invasion (in mm) in diagnostic and RVT specimen

	Diagnostic specimen*		**RVT specimen¶**	
	N		**N**	
Tumor width, in mm, median (range)				
Biopsy	5	11 (2 – 15)	5	20 (5 – 30)
LLETZ	36	8 (2 – 21)	15	8 (1 – 20)
Conization	14	7.5 (4 – 18)	3	9 (1 – 15)
Total	55	8 (2 -21)	23	9 (1 – 30)
Depth of tumor invasion, in mm, median (range)				
Biopsy (N4)	4	2 (2 – 10)	5	4 (2 – 7)
LLETZ	37	4 (2 – 21)	15	6 (1 – 12)
Conization	18	4.5 (2 – 9)	3	4 (3 – 6)
Total	59	4 (2 – 21)	23	5 (1 – 13)

*The total number of biopsies, LLETZ and conizations was 7, 40 and 20, respectively, no information on width and depth of tumor in the diagnostic specimen was available in some cases.
¶27 patients had residual tumor in RVT specimen, but no information on residual tumor size was available in 4 cases.
Abbreviations: LLETZ, large loop excision of the transformation zone.

Intra-, peri- and postoperative outcome

Median operative time (PLND and RVT together) was 353 min. (range 248-490 min), median blood loss (PLND and RVT together) 300 mL (range 50-1550 mL), and intra-operative complications included bladder lesions (4.5%), ureteric lesions (1.5%) and blood loss over 1000 mL (4.5%) (Table 3). The most common postoperative complications were bladder dysfunction (13.4%) and cervical stenosis (8.9%). All patients with stenosis underwent therapy (dilatation or hysteroscopy) to open

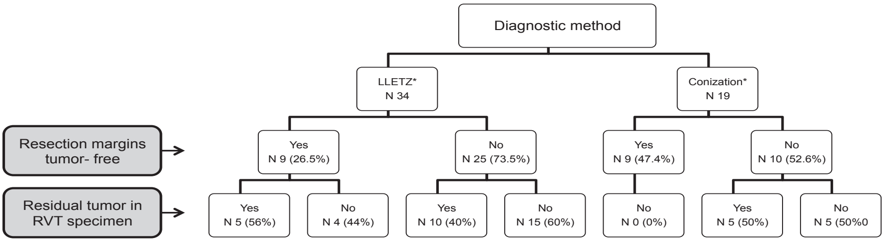

Figure 1: presence or absence of residual tumor Diagram illustrating the presence or absence of tumor in the specimens obtained at RVT in relation to the state of the resection margins in the diagnostic specimens. *A LLETZ was performed in 38 cases, and a conisation in 19 cases, but no information was available on the state of the resection margins of the diagnostic specimen in 5 LLETZ and 1 conization. Biopsies (N 6) are not included in the diagram. Abbreviations: LLETZ, large loop excision of the transformation zone; RVT, radical vaginal trachelectomy.

the cervical canal. In two cases repeated hysteroscopy (up to three times) was needed to obtain patency. In one case a levonorgestrel-IUD was inserted after three dilatation procedures to avoid re-stenosis and prevent dysmenorrhoea.

Pathology

Residual tumor was present in the RVT specimen in 29 of 67 cases (43%). Median specimen tumor size (width) was 9 mm (range 1-30mm). Median resection margin was 7.4 mm (range 2-15mm).

The relation between the state of the resection margins in the diagnostic specimens and the presence of residual tumor in the specimens obtained at RVT is illustrated in Figure 1. Information on the state of the resection margins was available in 34/40 LLETZ and in 19/20 conizations. Nine out of 34 LLETZ specimens had tumor-free resection margins, but in 5(56%) of these cases residual tumor was present in the RVT specimen. None of the 9 conizations with free resection margins (47.4%) had residual tumor in the RVT specimen. Conversely, 5/10 conizations with positive margins showed residual tumor in the RVT specimen. No correlation was found between median tumor width (<8mm or ≥8mm) or median tumor depth (<4mm or ≥4mm) in the diagnostic specimen and presence of residual tumor in the RVT specimen, analyzed in the total population, and in the subgroup of patients that were diagnosed by LLETZ or by conization. Furthermore, ROC analysis of tumor width or tumor depth in the diagnostic specimen in relation to presence of residual tumor in the RVT specimen in the total population and in the subgroup of patients that were diagnosed by LLETZ or by conization did not yield a significant cut off value.

Lymph nodes were negative in all cases but one. In this one case, the patient had a micrometastasis in an external iliac lymph node, detected by immunohistochemistry

(IHC) staining, and consisting of a cluster of cells with a diameter of 69.7µm. Taking into consideration the small size of this metastasis and the absence of other risk factors for recurrence of disease in a nulliparous patient who had a strong desire to preserve fertility no adjuvant treatment was given. The patient has no evidence of disease after 70 months of follow-up, and conceived twice after RVT, resulting in the delivery of a healthy baby in the third trimester of pregnancy.

Table 3. Intra and postoperative complications in the total population (N = 67)

	N	%
Intraoperative		
Bladder lesion	3	4.5
Urether lesion	1	1.5
Blood loss ≥ 1000 ml.	3	4.5
Postoperative		
Bladder dysfunction	9	13.4
Urinary tract infection	3	4.5
Neuropathy	1	1.5
Infection non-specified/fever	2	3.0
Cervical stenosis	6	8.9

Adjuvant treatment

Three patients received adjuvant treatment. In one case, a narrow resection margin, LVSI, and subepithelial (vaginal) tumor growth was observed; the patient received chemoradiation. Another patient presented with an undifferentiated carcinoma of 30 mm in its greater diameter, and positive resection margins in the RVT specimen; she also received chemoradiation. The third patient had a clear cell carcinoma and narrow resection margins in the RVT specimen. The patient underwent a laparoscopic hysterectomy, and received adjuvant radiotherapy. A fourth patient was offered adjuvant therapy but she refused and recurred: this case is discussed separately.

Recurrences and mortality

Median follow-up time was 60 months (range 12 -122 months). Three patients (4.5%) had a recurrence during follow-up; the first patient after a disease-free period of 38 months. She underwent a hysterectomy because of dysfunctional bleeding with no suspicion of recurrence, but final pathology showed a recurrence in the uterus. She underwent adjuvant radiotherapy and showed no evidence of disease at close of study. The second patient underwent a RVT but final pathology showed a tumor diameter of 27 mm and resection margins less than 5 mm. A radical hysterectomy was performed, but due to technical difficulties aborted and adjuvant chemo-radiation was advised. She refused however, and was lost to follow up for 46 months, after which a recurrence was diagnosed. Chemotherapy had been started at close of study. The third patient recurred after a disease-free period of 20 months, only one month after a Caesarean section for a healthy baby was performed. She received neo-adjuvant chemotherapy and a debulking comprising a radical hysterectomy with a resection of the distal part of the ureter, and a resection of the rectosigmoid with a colostomy. Furthermore, she received radiotherapy and was disease-free for 13 months at close of study.

Pregnancy outcome

Three out of the 67 women included in the study had no desire to preserve fertility, but wanted to keep their uterus for emotional reasons, three had adjuvant treatment after RVT and two were already pregnant when RVT was performed. Of the remaining 59 patients, 22 (37%) had no immediate desire to become pregnant, and 37 (63%) attempted to conceive. Of these 37 patients, 18 (48.6%) were treated for subfertility. However, in only three cases the subfertility was due to cervical stenosis and thus directly attributable to the RVT, whereas in all other cases pre-operative subfertility or other factors (i.e. male factor) were present. Seven out of 18 patients became pregnant after subfertility treatment, resulting in two healthy babies, two immature deliveries (15 and 20 weeks of gestation) and four first-trimester miscarriages. In total, 31 pregnancies were observed after the RVT procedure of which 2 women were already pregnant at the time of the surgical treatment and one patient was 30 weeks pregnant at close of study. Three pregnancies were terminated for non-medical reasons. Twenty healthy babies were born from 30 evaluable pregnancies (Table 4). The third trimester live birth rate was 19/30 (63.3%), with one healthy baby born at 27 weeks gestation. Thirteen out of 30 pregnancies (43.3%) culminated in healthy delivery at term.

Table 4. Number and outcome of pregnancies in the study population (N 61)*

Pregnancies¶	< 14 weeks§	14-28 weeks†	>28 weeks	Healthy offsprings
31	9 (29%)	2 (6.5%)	19 (61.3%)	20 (64.5%)

* From the 67 patients in the study population three had no desire to become pregnant (but wanted to keep their uterus), and three had adjuvant treatment after RVT.
¶Two of the patients were already pregnant when surgery was performed; one additional patient was 30 weeks pregnant at close of study.
§Includes two undesired pregnancies, which were terminated.
†One healthy offspring.

Discussion

In the Netherlands, the results of the RVT procedure are in agreement with those reported in the literature; our study shows that the procedure itself is safe and has a good long-term oncological outcome. Our recurrence rate is in line with data reported in the literature and no deaths have occurred during follow up [3].
The low number of recurrences in our study and absence of deaths may be partly due to the strict selection criteria applied for RVT. One of the selection criteria was tumor size under 2 cm, which is associated with a low recurrence rate [3,9,10,11]. In our series, none of the patients had parametrial involvement, but all were small stage IB1 or IA2 tumors. Only three patients required adjuvant treatment. One patient had a micrometastasis in a sentinel lymph node and did well without adjuvant therapy, and one patient refused adjuvant therapy and was diagnosed with a recurrence after 46 months of follow-up.
As summarized by Beiner et al. and Plante [5,8], RVT is a feasible procedure for patients with early stage cervical carcinoma who wish to preserve fertility. In our group, fertility results were comparable with earlier reports [12,13]. In three cases subfertility was directly attributable to cervical stenosis, and in 6 cases dilatation of the cervix was necessary. Leaving a Foley cathether in the uterus after surgery for a longer period of time (i.e. 2 weeks instead of 2 days) may prevent cervical stenosis, but numbers were too small for statistical analysis. Published results show that preterm delivery rate (<37 weeks) after RVT is 28%, much higher than in the general population (~9%), but only 12% of pregnancies will end in significant prematurity (<32 weeks) [3,5]. In the present study, the preterm delivery rate (<37 weeks) was 38.8%., Although this is a higher rate, only 14.2% culminated in significant prematurity which is in accordance with the above mentioned 12%. Overall, 43.3% of evaluable pregnancies ended in the birth of a healthy offspring at term, comparable to earlier reports. [12,13]
The high rate of preterm delivery is probably due to the removal of a significant part of the cervix, which reduces its mechanical support. Moreover, a shorter cervical canal may enable ascending infections, which can cause premature rupture of membranes and lead to preterm delivery [14,15].
Less aggressive surgery (i.e. conization) could be as effective in terms of disease-free and overall survival and could possibly lead to better obstetric outcome than RVT in patients with small invasive tumors. Arguably, in a number of our patients a large conization could possibly have been sufficient to eliminate the tumor. [16,17,18]. In our study, 14/20 (70.0%) patients who had had a conization did not

show residual tumor in the RVT specimen, which is in accordance with the 62-67% reported by Plante [5,7,19]. The presence of residual tumor in the RVT specimen did not correlate with the width and depth of the tumor in the conization specimen, suggesting that the need for RVT cannot be predicted by the magnitude of the lesion in the diagnostic specimen. None of the 9/19 (47%) diagnostic conizations that had free resection margins had any residual tumor in the RVT specimen, suggesting that an ample conization, which is performed with curative intent, may suffice as treatment. However, in 10 cases (52.6%) conization resection margins were not free of tumor, and would have required a second conization or trachelectomy (technically more difficult after a conization), to provide certainty that the tumor had been eradicated. Only 5 (50%) of these 10 patients (26.3% of all patients that had a diagnostic conization) had residual tumor in the RVT specimen. Up to date, there are no prospective data comparing conization with RVT.

As shown in our data, the method of diagnosis was not uniform. In 60 out of 67 (89%) cases an excisional technique was performed to gain histological proof of cervical carcinoma, and only in 11% a biopsy was performed. Accurate assessment of the total tumor size (width and depth) is often problematic after LLETZ, as it may involve adding together measurements obtained from individual tissue fragments. This may lead to over- or underestimation of the total tumor diameter. As a maximum tumor size of 2 cm is an important inclusion criterion to safeguard the oncological outcome, as well as to avoid the necessity of further surgery and adjuvant treatment, a colposcopy guided biopsy with estimation of the tumor size by inspection, and possibly by MRI, may provide the best diagnostic approach.
In the present study, LVSI in the diagnostic specimen was not an exclusion criterion to perform RVT. Although LVSI was observed in 24% of the diagnostic specimens (Table 1), up to date only three recurrences have been observed during follow up (in one case LVSI was present, one unknown, and one absent). Another issue is whether age should remain an inclusion criterion for RVT. In our opinion, a maximum age of forty years can be abandoned as long as the maximum tumor size does not exceed 2 cm, as this will ensure the same survival as the more radical Wertheim-Meigs (Okabayashi) technique, but with lower morbidity [3,8,11]. Age as inclusion criterion is closely related to the procedure having the objective to preserve fertility. In our study, a maximum of 40 years of age and preservation of fertility were strict inclusion criteria. Interestingly, only 67% of patients tried to conceive after therapy. Approximately 20% of the patients in our study were

≤29 years of age, and for this group of younger women starting a family may not yet have been an issue. Other factors that could have influenced the decision to become pregnant are the time needed to recover physically and emotionally from surgery together with the relatively short follow-up time of our study [20]. Both the surgery and the disease itself may lead to sexual or psychological problems (fear), and abandonment of the wish to bear a child. If preservation of fertility is not an issue, and considering the excellent oncological outcome in our study, age could be omitted as inclusion criterion for RVT.

In conclusion, our data, in conjunction with the data published worldwide, show that RVT deserves a place as standard therapy for early stage cervical cancer with a tumor size equal or under 2 cm, irrespective of the patients age or their wish to preserve fertility. Our study suggests that conization combined with lymphadenectomy may be insufficient treatment for this group of patients. This suggestion requires further investigation.

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Discussion and conclusion

For over a century, the treatment of choice for early stage cervical cancer has been an open radical hysterectomy and pelvic lymph node dissection, the Wertheim-Meigs (Okabayashi) operation [1,2,3]. The technique has good oncological results and can be universally performed. Modifications of the original technique, described by Wertheim [1], such as the introduction of nerve-sparing techniques have reduced part of the associated morbidity [4,5]. However, it is still a treatment associated with loss of fertility and significant morbidity. Furthermore, in case of small early stage tumors (i.e. under 2 cm in size) patients may be overtreated, as less extensive procedures, such as radical vaginal trachelectomy (RVT) instead of radical hysterectomy and sentinel lymph node (SLN) dissection instead of full lymph node dissection, seem to yield similar disease outcome [6,7]. Conversely, patients with slightly more advanced tumors treated with standard radical surgery may require adjuvant radiotherapy, due to e.g. the presence of tumor positive lymph nodes, and thus will be subject to the morbidity of both surgery and radiation. For the Western World, the real challenge in the treatment of early stage cervical cancer is not only to improve the already excellent cure rates, but to reduce morbidity and retain fertility whenever possible.

Conservation of childbearing capacity without compromising oncological outcome is relevant for younger women with early stage cervical cancer. The increasing availability of tools for an accurate assessment of tumor size and lymph node status allows for a better selection of treatment options. It may now be time to leave the *one size fits all* approach where one operation will suit the majority of patients, and elect a novel one, where a patient will be stratified for tailored treatment through a step-by-step approach to determine the extent of disease and then choose the adequate and least morbid treatment.

Conclusions derived from the present thesis

Part I: Serum tumor markers as predictors for occult disease in early stage cervical cancer

The use of serum tumor markers to define treatment strategy is not well established in early stage cervical cancer. Accepted prognostic factors as defined by the Gynecologic oncology Group (GOG) are tumor size, lymph node status, stage, bilateral disease, age and performance status, but not serum markers [8]. SCC-Ag, the best studied serum tumor marker in cervical cancer, is not routinely measured in all clinical centers in the Netherlands. According to the Dutch National Guidelines [9] there is not enough information on the value of SCC-Ag as a predictive marker

for lymph node metastases [10,11,12]. In a **retrospective study** (Chapter 2, this thesis) we found that the addition of CYFRA 21-1 to SCC-Ag identified a group of lymph node negative patients with elevated markers and a relatively poor disease outcome, suggesting the presence of occult disease in these patients.
Furthermore, in a **second** study (chapter 3) in early stage cervical cancer patients undergoing SLN dissection and/or pelvic lymphadenectomy we found that an SCC-Ag serum level > 1.65 ng/mL identified patients with negative lymph nodes with a disease outcome similar to that of patients with positive lymph nodes. These patients with an elevated SCC-Ag could represent a subgroup of patients with submicroscopic (occult) disease who may potentially benefit from a full lymphadenectomy in spite of a negative SLN procedure. Furthermore, the SLN procedure, which permits an extensive histopathologic analysis of the lymph nodes that is not viable in a full lymphadenectomy, facilitates the possibility of detecting micrometastatic disease and even clusters of a few tumor cells that may go otherwise undetected. The prognostic importance of occult disease is supported by recent findings from our group that patients with negative or macrometastatic SLN do not profit from additional LND, but survival of patients with micrometastases, including isolated tumor cells, is improved when more than 16 additional pelvic lymph nodes are removed [13].
In this context, the utility of SCG-Ag and CYFRA 21-1 to define occult disease and prognosis should be evaluated in the frame of randomized clinical trials studying prognostic factors and SLN procedure in relation to treatment in early stage cervical cancer.

Part II. The use of minimal invasive surgical techniques to tailor treatment of early stage cervical cancer

As lymph-node positive patients will require (adjuvant) radiotherapy, lymph node assessment is of paramount importance to determine the mode of primary treatment. In this way, double modality treatment with the associated extended morbidity can be avoided. With this in mind the use of diagnostic tools to evaluate lymph node status becomes increasingly important.
In early stage cervical cancer, diagnostic tools such as physical examination, serum tumor markers, CT, MRI and PET scan, are of limited use to define nodal status [14]. The **third** study in this thesis (chapter 4) is a systematic review of the diagnostic performance of SLN detection for minimal invasive assessment of nodal status in early stage cervical cancer, and analyses which technique (blue dye, Technetium-

99m colloid or the combined method) is best in terms of detection rate and sensitivity. We found a SLN detection rate of 97% and sensitivity of 92% when a combination of patent blue and Technetium-99m colloid (^{99m}Tc) is used.
Since then, many articles have been published regarding the use of SLN procedure in cervical cancer. In 2012, Cibula e.a. found that detection of bilateral SLN and ultrastaging will decrease false negativity to 2,8% [15]. Sentinel node detection contributes towards ultrastaging patients, and the presence of micrometastases was found to be an independent prognostic factor for overall survival with the same hazard ratio as macrometastases [15]. Because of the smaller number of lymph nodes involved, the SLN procedure allows for a more intensive search for micrometastases (multiple sectioning, addition of immunohistochemistry). This is supported by Vicus and colleagues who found that SLN biopsy increases the detection rate of metastases up to 2,8 fold compared to conventional pelvic lymph node dissection [16].
To date, the SLN procedure is the most sensitive method to detect lymph node metastases, especially in the case of small stage IB1 tumors [17]. Full lymphadenectomy will be unneccesarily performed in about 80% of patients, as less than 20% of early stage cervical cancer patients will have positive nodes [18]. Full lymphadenectomy is associated with a number of short and long term complications, such as lymphedema and lymfocele formaton [19]. However, the standard use of SLN should follow a strict procedural protocol as recent reports on its use show conflicting results. In a multicenter German study there was not only an overall low, but especially also a wide variation in detection rate among the participating centers, of whom some only contributed a few cases and therefor had little experience with the procedure [20]. Additionally, in a multicenter prospective study of SLN in 139 patients with early stage cervical cancer (SENTICOL study), Bats e.a. found a poor predictive value of intraoperative examined SLN by frozen section or imprint cytology (performed in 74.3% of patients), with only 5 positive lymph nodes detected (20.7% per node sensitivity) compared to 22 positive lymph nodes in the final pathology. However, the nodes were not examined uniformely, and in many cases no serial sectioning of the SLN was performed [7]. The importance of intraoperatively performed serial sectioning has recently been established by Gortzak-Uzan e.a. who found a much higher sensitivity (11/14 positive nodes, 78.6 %) compared to the SENTICOL study (5/22 positive nodes, 22.7 %) [21].
Ultimately, Cormier e.a. have shown that by applying a surgically defined algorithm the sensitivity for positive lymph nodes is 100%. The surgical algorithm consists of 1. SLNs are removed and submitted to ultrastaging; 2. any suspicious

LN is removed regardless of mapping; 3. if only unilateral mapping is noted, a contralateral side-specific pelvic LND is performed (including inter-iliac nodes); and 4. parametrectomy en bloc with primary tumor resection is done in all cases (as parametric lymph nodes can be overseen when adjacent to the primary tumor and as such not separately visible by a probe). The sensitivity of SLN alone was 21/24 positive lymph nodes (87.5%). The authors propose that use of the algorithm eliminates an unneccesary LND in 75% of patients [22]. It may be time to rely only on SLN dissection instead of a full lymphadenectomy for the establishment of LN status in early stage cervical cancer, when such a strict algorithm is used.

The **fourth** study (chapter 5) evaluates retrospectively the safety and yield of laparoscopic lymphadenectomy compared to a laparotomy to obtain lymph nodes. Concerns have been raised that laparoscopic radical surgery might induce more and differently located recurrences compared to open surgery. In this context, recently a case report of a port-site metastasis after *robotic-assisted* laparoscopic radical hysterectomy in early stage cervical cancer has been published [23]**.** Although, according to the author, port-site metastases are very rare and only 25 cases so far have been reported in literature, it still could be an unwanted side-effect of a laparoscopic approach.

Our study shows that a laparoscopic lymphadenectomy has no detrimental effect on outcome in terms of overall and disease specific survival compared to the classical open lymphadenectomy. No port-site metastases were found and recurrence patterns did not differ from the abdominal route. Laparoscopy is an efficient and minimally invasive way of obtaining lymph nodes. It can be safely applied to early stage cervical cancer. Recent studies support these findings, as laparoscopic radical hysterectomy has shown to be equal in terms of survival and recurrence-free interval, but with fewer post-operative complications and a faster recovery time [24]

In the **fifth** study (chapter 6) we analysed the long term oncologic and obstetric outcome of radical vaginal trachelectomy (RVT) for the first 67 cases performed in the Netherlands to illustrate the feasibility of the implementation of minimal invasive, fertility preserving surgery in early stage cervical cancer. For small stage IB1 tumors, up to 2 cm a RVT is a well-established option, with excellent oncological results that are comparable to the Wertheim- Meigs procedure [25]. Up to now, a maximum age of 40 and the wish to retain fertility were applied in most cases as selection criteria for RVT. These selection criteria should actually be abandoned as soon as an equal disease-free and overall survival between the two surgical methods will have been established. This would need a randomized trial in patients who obviously do not wish to preserve their fertility. As only 67% of patients in our group tried to conceive after therapy, an absence of a wish to conceive does not seem a valid argument to refrain from this therapy. Considering the good oncological results, as long as a maximum tumor diameter of 2 cm is applied as an inclusion criterium, age is also no longer a consideration for the choice of RVT.

To date, for tumors above 2 cm of diameter a radical hysterectomy remains the best option, as radical vaginal trachelectomy has shown a higher recurrence rate in this group [25,26]. Alternatively, a radical abdominal trachelectomy might be performed with possibly equal oncological results as a radical hysterectomy, although neo-adjuvant chemotherapy may be necessary in these cases. [27] One disadvantage of the abdominal approach is that it is done through conventional laparotomy, losing the benefits of a mininimal invasive approach, although robot assistance makes a laparoscopic approach also feasible [28,29,30] An even more important disadvantage is that the pregnancy rate after the abdominal approach is lower than after vaginal radical trachelectomy although a recent publication showed similar results to those obtained with RVT [25,31].

At this point in time, laparoscopic radical hysterectomy or robot-assisted radical hysterectomy is the logical choice for miminally invasive treatment of tumors exceeding 2 cm in size. Today, a robot-assisted radical hysterectomy seems the best choice, as it offers advantages both to the patients (shorter hospital stay), and to the surgeons (better ergonomics and a shorter learning curve than the conventional laparoscopic approach) [32,33,34].

Future developments

As discussed above, an adequate choice of therapy in early-stage cervical cancer is defined by two main determinants: lymph node status and tumor size. Whenever possible, a SLN (without full lymphadenectomy) and minimal invasive surgery should be the first choice. Following the available literature and the results of this thesis, patients can be stratified for therapy using a step-by-step approach that takes into account the results of physical examination, imaging and a tumor marker (SCC-Ag).

A step-by-step approach flowchart

The above mentioned could result in a flowchart (Fig. 1) with SCC-Ag integrated into it and used in combination with a sentinel node procedure to tailor treatment towards minimal invasive therapy when possible. Thus, an elevated SCC-Ag may indicate occult disease and warrant a full lymphadenectomy even in the presence of a negative SLN. In this respect, the possible role of CYFRA-21 is open to further study, and may offer additional information to that obtained with SCC-Ag alone (Chapter 2). After FIGO staging and imaging, patients should be devided into two groups, marker-negative (SCC-Ag below 1.65 ng/mL) and marker-positive (SCC-AG above 1.65 ng/mL) group. Marker-negative patiens may undergo a laparoscopic sentinel lymph node procedure only, whereas marker-positive patients should undergo a full laparoscopic lymphadenectomy in addition to a sentinel lymph node procedure.

The first group (marker-negative) will undergo further surgery according to tumor size when SLN are tumor-negative. In the second group (marker-positive) one could argue that only when *all excised* lymph nodes have been examined patients will undergo further surgery. This could entail a radical vaginal trachelectomy or radical hysterectomy *in a second session*. However, whether surgery should be performed in one or two sessions is still open for discussion and this has not been addressed in this thesis.

Lymph node positive patients will receive chemoradiation. Although it has been suggested by Höckel that more radical dissection of lymphoid tissue (Total MesoMetrial Resection, TMR) would abolish the necessity for adjuvant treatment [35], the outcome of a current multicenter German study should indeed confirm whether this is a safe approach. Until such time, all patients having lymph node metastases will receive adjuvant therapy. Although completion by radical hysterectomy has been advocated in selected cases [36], it should be argued that, chemoradiation only will offer the same survival with less morbidity than a combination of radical surgery and radiation therapy [37,38]

Other treatment strategies for early stage cervical cancer

The step-by-step approach applies mainly to early stage cervical cancer. It illustrates, how stage IA2-IB1 patients can be treated according to a specified regimen to enhance uniformity and to offer this group of patients treatment tailored to lowest morbidity but still oncologically safe. It is of note, though, that many of the approaches mentioned in this thesis can only be applied in expert centres, mostly situated in the Western Countries, and by trained surgeons. The limited access to these techniques means that open radical hysterectomy as a treatment for early stage cervical cancer will continue to be used in a major part of the world. Furthermore, the step-by-step approach is only a current suggestion in a rapidly evolving field. Examples of (near) future additions to tailored surgical treatment are the use of robotic surgery [39] and the use of a conization combined with a sentinel node procedure when tumor size does not exceed 2 cm. [40] Another novel strategy is the use of neoadjuvant chemotherapy to reduce tumor size in order to offer patients with tumors larger than 2 cm a RVT, or even a conization. These options are currently under evaluation, and may be able to reduce morbidity even further [27,41]. Targeted anti-viral therapy, such as the use of a HPV16 E6 and E7 synthetic long peptides vaccine as part of vaccine-induced antitumor therapy, shows promising results [42]**,** but is not yet available for routine use**.** These vaccines are also being tested to control CIN 2/3 progression as as a treatment to avoid the emergence of cervical cancer [43,44]. However, at this point in time patient-tailored treatment with emphasis on minimal invasive surgical therapy remains the best choice to avoid morbidity associated with the treatment of cervical cancer.

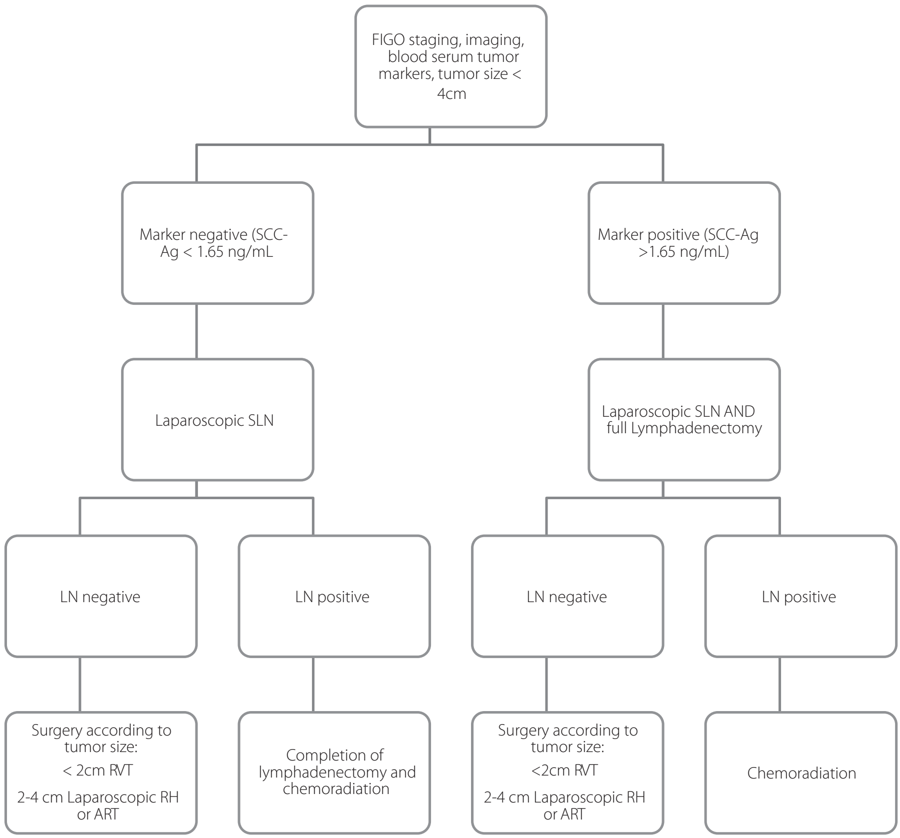

Figure 1. A step-by-step approach to patient-tailored treatment.
(LN: lymphnodes, SLN: sentinel lymph node, RVT: radical vaginal hysterectomy, RH: radical hysterectomy, ART: abdominal radical trachelectomy)

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Summary

In **Chapter 1** we give an outline of the current FIGO staging system with its limitations to detect lymph node metastases. We summarise the current imaging techniques, each with its own merits and drawbacks, to diagnose extent of disease in early stage cervical cancer, and introduce surgical staging. Current treatment modalities such as the standard Wertheim Meigs operation and chemoradiation are addressed and treatment advantages and morbidity of each procedure are summarised in a table. Finally, the outline of this thesis is presented. The objective of the present thesis is to investigate the use of tumor markers and minimal invasive surgery to define patient-tailored treatment in early stage cervical cancer.
In **Chapter two** we investigated if a combination of pretreatment blood serum markers (SCC-Ag, CYFRA 21-1, CA 15-3 and CA125) could identify patients with occult disease in squamous cell cervical cancer. Univariate analysis showed SCC-Ag, CYFRA 21-1 and CA 15-3 to be strongly associated with overall and disease-free survival, and lymph node status was identified in multivariate analysis as the strongest predictor, followed by CYFRA 21-1 and CA 15-3. Clinical cut-off values for each marker were defined, and showed that stage IBI patients with positive SCC-Ag *and* CYFRA 21-1 markers had significantly lower overall and disease-free survival than all other stage IBI patients. Patients with a bulky tumor or positive SCC-Ag *and* CYFRA 21-1 had also significantly poorer disease-free and overall survival compared to *all other* patients in the same group. We concluded that this combination of SCC-Ag and CYFRA 2-1 could help identify patients with occult disease requiring adjuvant therapy such as chemoradiation.
In **Chapter three** we analysed pretreatment SCC-Ag levels, lymph node status and disease outcome in early stage cervical cancer. We found that SCC-Ag levels were higher in patients with positive lymph nodes compared to patients with negative lymph nodes. We established a cut-off level of 1.65 ng/mL that predicted positive lymph nodes with an accuracy of 76% in stage IB1, but only 53% in IB2 and IIA. Overall survival of patients with negative lymph nodes but elevated SCC-Ag levels was similar to patients with positive lymph nodes, suggesting that patients with elevated SCC-Ag levels may benefit from a full lymphadenectomy even when a sentinel lymph node procedure indicates no LN metastases.
Chapter four is a systematic review addressing the diagnostic performance of the sentinel lymph node procedure in early stage cervical cancer in relation to the technique used: blue dye, Technetium-99m colloid, or a combination of both. We found that the combined technique performs best in terms of detection rate (97%) and sensitivity (92%), and concluded that according to the literature (reviewed

until 2007) sentinel node procedure is a reliable method to detect lymph node metastases in early stage cervical cancer.

Chapter five investigates the possible detrimental effects of the introduction of laparoscopy for lymph node dissection in combination with an open radical hysterectomy compared to the standard procedure of open radical hysterectomy and lymph node dissection, in patients treated at our centre (Free University medical centre Amsterdam) from 1994 onwards. Seventy-six patients underwent laparoscopic and 93 open lymph node dissection. We found no difference in complication rates, but, as expected, operating time was longer in the laparoscopy group. In patients with tumor negative lymph nodes, more lymph nodes were resected through laparoscopy (median 26) than through laparotomy (median 21). No difference in disease-free or disease specific survival between the two groups was found, and we concluded that laparoscopy can be safely applied to the treatment of early stage cervical cancer.

Chapter six serves as an example of the implementation of a minimal invasive technique in early stage cervical cancer. The Dutch results of the RVT procedure performed from its introduction in 2000 until 2008, with follow-up until January 2012 are described. We evaluated 67 RVT procedures, with a median follow up of 60 months. Thirty-one pregnancies occurred, resulting in 20 healthy babies. Three recurrences and no deaths occurred. Our results are comparable to those described in the literature. Of the diagnostic specimens, 10 out of 19 conizations showed tumor-positive margins. We concluded that RVT is a safe way to treat small (less than 2 cm) early stage cervical cancer, and that a simple conisation is not yet safe as an alternative treatment.

Chapter seven places the treatment of early stage cervical cancer in its historical perspective and summarizes the options and drawbacks of the current standard therapy. Results of the present thesis are integrated into a step-by-step algorithm as an aid to establish patient-tailored treatment of early stage cervical cancer. The emphasis is laid on the feasibility of employing minimal invasive techniques to reduce morbidity and retain fertility without compromising oncological safety. Some future approaches for the treatment of early stage cervical cancer are briefly mentioned.

Samenvatting in het Nederlands

In **hoofdstuk 1** geven we een overzicht van het huidige FIGO stagerings systeem met zijn beperkingen om lymfkliermetastasen aan te tonen. De huidige beeldvormende technieken worden samengevat, met van elk de voor- en nadelen met betrekking tot het aantonen van uitbreiding van ziekte, en wij introduceren de chirurgische stagering. Huidige gangbare behandelingsmodliteiten zoals de standaard Wertheim- Meigs operatie en chemoradiatie worden belicht, en van elke procedure worden de voor-en nadelen samengevat in een tabel. Tenslotte wordt de opzet van dit proefschrift gepresenteerd. Het doel van dit proefschrift is om het gebruik van tumor markers en minimaal invasieve chirurgie te onderzoeken om zo tot een per patient aangepaste therapie te komen bij een vroeg stadium baarmoederhalskanker.

In **hoofdstuk 2** hebben we onderzocht of een combinatie van serum tumor markers (SCC-Ag, CYFRA 21-1, CA 15.3, en CA 125), afgenomen vóór aanvang van de therapie, in staat was om patienten met verborgen ziekte bij vroeg stadium baarmoederhalskanker aan te tonen. Univariate analyse toonde aan dat SCC-Ag, CYFRA 21-1 en CA 15.3 sterk geassocieerd zijn met overleving en ziekte-vrije interval, en bij multivariate analyse werd lymfklierstatus als sterkste voorspeller aangetoond, gevolgd door CYFRA 21-1 en CA 15-3. Klinische afkapwaardes voor elke marker werden vastgesteld, en deze toonden aan dat patiënten met een stadium IBI *en* positieve SCC-Ag en CYFRA 21-1 markers een significant kortere overleving en ziekte-vrij interval hadden dan alle andere stadium IBI patiënten. Patiënten met een *bulky* tumor of positieve SCC-Ag en CYFRA 21-1 hadden bovendien een significant kortere ziekte-vrije en algemene overleving wanneer zij werden vergeleken met *alle andere* patiënten in dezelfde groep. We hebben geconcludeerd dat deze combinatie van SCC-Ag en CYFRA 21-1 patiënten kan identificeren welke adjuvante therapie nodig hebben, in de vorm van chemoradiatie.

In **hoofdstuk 3** hebben we een analyse verricht van vooraf bepaald SCC-Ag, lymfklierstatus en ziekte uitkomst bij een vroeg stadium baarmoederhalskanker. De waardes van SCC-Ag bleken hoger bij patiënten met positieve dan bij patiënten met negatieve lymfklieren. We hebben een afkapwaarde van 1,65 ng/mL vastgesteld welk in geval van een stadium IBI in 76% in staat was positieve klieren te voorspellen, echter slechts in 53% van de gevallen bij een stadium IB2 of IIA. Patiënten met een verhoogd SCC niveau maar negatieve klieren bleken een vergelijkbare overleving te hebben vergeleken met patiënten met positieve klieren. Dit zou kunnen betekenen dat patiënten met een verhoogd SCC-Ag niveau profijt zouden kunnen hebben van een volledige lymfklierresectie, zelfs wanneer een schildwachtklier procedure geen lymfkliermetastasen heeft aangetoond.

Hoofdstuk 4 is een *systematic review* welk de diagnostische kracht van de schildwachtklier procedure onderzoekt in relatie tot de gebruikte techniek: patent blauw, Technetium-99m colloid, of een combinatie van deze twee. Wij vonden dat de gecombineerde techniek het beste een schildwachtklier detecteert (97%), en de beste sensitiviteit had (92%), en concludeerden dat volgens de literatuur (opgezocht tot 2007) de schildwachtklierprocedure een betrouwbare methode is om lymfkliermetastasen aan te tonen bij een vroeg stadium baarmoederhalskanker.

Hoofdstuk 5 onderzoekt of de introductie van laparoscopie om lymfklieren te verkrijgen, gecombineerd met een open radicale baarmoederverwijdering vergeleken met de standaard open procedure voor zowel klieren als baarmoeder een mogelijk schadelijk effect had, voor patiënten die in ons centrum (Vrije Universiteit medisch centrum, Amsterdam) vanaf 1994 op deze manier behandeld werden. Zesenzeventig patiënten ondergingen een laparoscopische lymfklierdissectie, tegen 93 open lymfklierdissecties. We vonden geen verschil in complicaties, maar de operatietijd was, zoals verwacht, langer in de laparoscopie groep. In de groep zonder lymfklier metastasen werden door middel van laparoscopie meer klieren (mediaan 26) verkregen dan middels laparotomie (mediaan 21). Er werd geen verschil gevonden in ziekte vrij interval noch overleving. We hebben geconcludeerd dat laparoscopie veilig gebruikt kan worden bij een vroeg stadium baarmoederhalskanker.

Hoofstuk 6 dient als een voorbeeld hoe een minimaal invasieve techniek kan worden geïmplementeerd bij vroeg stadium baarmoederhalskanker. De Nederlandse resultaten van de radicale trachelectomie operatie vanaf de introductie in 2000 tot 2008 worden beschreven, met *follow-up* tot januari 2012. We hebben 67 RVT procedures geëvalueerd, met een mediane *follow-up* van 60 maanden. Er ontstonden 31 zwangerschappen, resulterend in 20 gezonde pasgeborenen. Er deden zich drie recidieven voor, maar geen sterfgevallen. Onze resultaten zijn vergelijkbaar met die zoals beschreven in de literatuur. Van het diagnostisch weefsel toonden 10 van de 19 conisaties nog tumor in de resectieranden. We hebben geconcludeerd dat de radicale vaginale trachelectomie een veilige methode is om een kleine (minder dan 2 cm. in diameter) vroeg stadium baarmoederhalskanker te behandelen, en dat een conisatie nog niet net zo veilig is als alternatieve behandeling.

Hoofdstuk 7 plaatst de behandeling van een vroeg stadium baarmoederhalskanker in zijn historische perspectief en vat de opties en nadelen van de huidige standaard therapie samen. Resultaten van het huidige proefschrift worden geïntegreerd in een stap-voor-stap algoritme om als hulpmiddel te dienen voor een per patient aangepaste therapie voor een vroeg stadium baarmoederhalskanker. De nadruk ligt op de mogelijkheden om minimaal invasieve technieken toe te passen en zo morbiditeit te verminderen en fertiliteit te behouden zonder dat dat ten koste gaat van de oncologische veiligheid. Enkele toekomstige benaderingen voor de behandeling van vroeg stadium baarmoederhalskanker worden kort genoemd.

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Curriculum vitae

Jonas van de lande werd op 11 oktober 1963 geboren in Amsterdam als zoon van psychiater Jan van de Lande en balletdanseres Nancy 't Hart. Al vroeg volgde een verhuizing naar Santpoort met een gelukkige jeugd rond Haarlem.
Na zijn eindexamen op het Kennemer Lyceum te Overveen in 1984 werd hij uitgeloot voor de studie Geneeskunde en startte met de studie Economie aan de Universiteit van Amsterdam. Later lukte het gelukkig wel om - met ups en downs - de studie Geneeskunde aan de UVA te volbrengen. Tegelijkertijd werkte hij van 1986 tot 1996 bij een beroemde Hifi-winkel in Amsterdam, waar hij veel leerde over de omgang met mensen. Van 1992 tot 1996 was hij tevens werkzaam als docent bij de Stichting Opleidingen Gezondheidszorg Amsterdam (S.O.G.A.). Vanaf 1996 werkte hij in de gynaecologie, eerst in het Andreas ziekenhuis in Amsterdam, later in het OLVG waar hij ook met zijn opleiding tot gynaecoloog begon (opleider: Dr. M. F. Schutte), later vervolgd in het AMC (opleider: Prof. Dr. O. P. Bleker). Na voltooien van de opleiding in het St. Lucas Andreas ziekenhuis te Amsterdam (opleider: Prof. Dr. F. Scheele) vervolgde hij op geweldig advies van collega dr. J. Dijkstra hij zijn weg als fellow Gynaecoloog met aandachtsgebied Oncologie (GOA) aan het VUmc medisch centrum te Amsterdam onder leiding van prof. dr. R.H.M. Verheijen, waar hij ook staflid was tot 2006 en een start werd gemaakt met dit proefschrift.
Vanaf 2006 is hij werkzaam als staflid in het Kennemer Gasthuis te Haarlem, als GOA en tevens met minimaal invasieve chirurgie als aandachtsgebied. Sinds 2009 is hij plaatsvervangend opleider, sinds 2011 ook lid van het stafbestuur van het Kennemer Gasthuis, en sinds 2012 tevens aktief als medisch manager van de vakgroep.

Hij is gelukkig getrouwd met Barbara Norg waarmee hij in Haarlem woont en is de trotse vader van Sophie, Tom, Wisse, Roos en Floor.

Jonas van de Lande was born on the 11th of October 1963 in Amsterdam as son of psychiatrist Jan van de Lande and ballet dancer Nancy 't Hart. Soon, the family moved to Santpoort, where he spent a happy youth in the area of Haarlem. After graduating at the Kennemer Lyceum in Overveen he was rejected based on random selection for Medical School and started a study Economy. Fortunately he was given a second chance and started Medical School at the University of Amsterdam, which he finished with ups and downs. From 1986 until 1996 he worked also at a famous Hifi store in Amsterdam, where he learned a lot about dealing with people. From 1992 until 1996 he also served as a teacher at the Stichting Opleidingen Gezondheidszorg Amsterdam (S.O.G.A.). In 1996 he started his career in Obstetrics and Gynecology as a senior house officer at the Andres hospital, Amsterdam. From 1997 on he worked at the Onze Lieve Vrouwe Hospital, Amsterdam where he started his specialist training (Dr. M. F. Schutte) , followed by the Academical Medical Center, Amsterdam (Prof. Dr. O. P. Bleker) and the St. Lucas Andreas hospital, Amsterdam (Prof. Dr. F. Scheele) where he completed his specialist training. Following the excellent advice of dr. J. Dijkstra he worked from 2003 as a fellow gynecologic oncology at the VU University medical center, Amsterdam (Prof. Dr. R. H. M. Verheijen), where he started with this thesis. Since 2006 he is a consultant gynecologist with main fields of interest oncology and minimally invasive surgery at the Kennemer Gasthuis, Haarlem, The Netherlands. Since 2009 he has been the associate specialist trainer, since 2011 member of the staff board, and from 2012 also the medical manager of the department of Obstretics and Gynecology.

He is happily married to Barbara Norg and is the proud father of Sophie, Tom, Wisse, Roos and Floor.

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