Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study

Michael Höckel, Benjamin Wolf, Katja Schmidt, Meinhard Mende, Bahriye Aktas, Rainer Kimmig, Nadja Dornhöfer, Lars-Christian Horn

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Leipzig School of Radical Pelvic Surgery (Prof M Höckel MD), **Department of Gynecology and Obstetrics** (B Wolf MD, Prof B Aktas MD, N Dornhöfer MD), **Institute of Anatomy** (K Schmidt RN), **Institute for Medical Informatics, Statistics and Epidemiology** (M Mende PhD), **and Division of Breast, Gynecological and Perinatal Pathology** (Professor L-C Horn MD), **University of Leipzig, Leipzig, Germany; Department of Gynecology and Obstetrics, University of Essen, Essen, Germany** (Prof M Höckel, Prof R Kimmig MD); **and Department of Gynecology and Obstetrics, Technical University of Munich, Munich, Germany** (Prof M Höckel)

Correspondence to: Prof Michael Höckel, Leipzig School of Radical Pelvic Surgery, University of Leipzig, Leipzig 04103, Germany **michael.hoeckel@uniklinik-leipzig.de**

Summary

Background Previous findings from our centre suggest that carcinoma of the cervix propagates within ontogenetic cancer fields, tissue compartments defined by staged morphogenesis. We aimed to determine whether surgical treatment that accounts for stage-associated, ontogenetic cancer fields and their associated lymphoid tissues results in locoregional tumour control without the need for adjuvant radiotherapy.

Methods We did the final clinical and histopathological evaluation of data from, the single-centre, observational, cohort study, the Leipzig School Mesometrial Resection Study. Patients of any age with stage IB1, IB2, IIA1, IIA2, or IIB cervical cancer (according to 2009 International Federation of Gynecology and Obstetrics [FIGO]) had total mesometrial resection or extended mesometrial resection and therapeutic lymph node dissection, done on the basis of ontogenetic cancer fields. We defined sentinel node, first-line, second-line, and third-line lymph node regions as progressive regional cancer fields. Primary outcomes were disease-specific survival and recurrence-free survival, and treatment-related morbidity (assessed with the Franco-Italian glossary). Applying Cox proportional hazard models, ontogenetic local (T) and regional (N) tumour staging was compared with pathological T and N staging. This trial is registered with the German Clinical Trials Register, number DRKS00015171.

Findings Between Oct 16, 1999, and June 27, 2017, 523 patients were treated per protocol and followed up for a median of 61·8 months (IQR 49·3–94·8). In 495 patients with cervical cancer treated with cancer field surgery, 5-year disease-specific survival was 89·4% (95% CI 86·5–92·4) and recurrence-free survival was 83·1% (79·7–86·6). In the per-protocol population of 523 patients, treatment-related morbidity comprised 112 (21%) grade 2 and 15 (3%) grade 3 complications. The most common moderate and severe treatment-related complications and sequelae were wound dehiscence (17 [3%]), hydronephrosis (17 [3%]), bowel obstruction (26 [5%]), and lymph oedema (33 [6%]). One patient (<1%), who received total mesometrial resection, died from postoperative brain infarction.

Interpretation Total or extended mesometrial resection with therapeutic lymph node dissection based on ontogenetic cancer fields results in good survival outcomes of patients with cervical cancer in our institution, but needs to be investigated further in multicentre trials.

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Introduction

Treatment of cervical carcinoma consists of surgery and radiotherapy for locoregional tumour control.[1] Based on a model of randomly diffusive local tumour spread, the aim of radical hysterectomy, the conventional surgical treatment for 2009 International Federation of Gynecology and Obstetrics (FIGO) stages IB1 and IIA1 cervival cancer, is to excise the malignant lesion with a circumferential wide margin of cancer-free tissue, preserving the adjacent bladder, ureters, rectum, and pelvic autonomic nerves.[2,3] The surgical anatomy of the subperitoneum covering the major procedural part of conventional radical hysterectomy is defined by ligaments and spaces, all of which are dissection artifacts rather than developmentally defined anatomical structures.[3] Systematic lymph node dissection or sentinel node biopsy is done as a means of accurate nodal staging.[4,5] For lymph node metastases, guidelines demand primary radiotherapy or chemo-radiotherapy to avoid postoperative radiotherapy, which would otherwise be necessary to achieve acceptable locoregional tumour control.[6] Neoadjuvant chemotherapy to downsize tumours is considered by some gynaecological oncologists as a treatment for advanced stage disease. However, in most centres, patients with stage IIB and higher cervical cancer are candidates for primary chemoradiotherapy.[7] Reported oncological treatment results are often blurred by the inaccuracy of staging with clinical and imaging methods, patient selection, retrospective recording, or excerpts from national or regional databases. For a more accurate assessment, complete pathological staging and prospective data acquisition are essential.[8,9] In one study of

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and Scopus between Jan 19, 1999, and Jan 19, 2019, for publications in English only using the following terms in various combinations: "cervical OR cervix", "carcinoma OR cancer", "FIGO stages", "histopathological risk factors", "(close) resection margin", "survival", "surgical therapy", "radical hysterectomy", "adjuvant radiation OR radiotherapy OR chemoradiation", "postoperative radiotherapy", "treatment-related morbidity", "complications", "Franco-Italian glossary", "pelvic lymph node dissection", "para(peri)aortic lymph node dissection", "pelvic lymph node metastases", "para(peri)aortic lymph node metastases", "local tumour spread", "regional tumour spread", "pelvic lymph node regions", "para(peri)aortic lymph node regions", and "pattern of lymph node metastases". Additionally, we searched the Cochrane library for meta-analyses of cervical cancer treatment and consulted the most recent national and international guidelines on cervical cancer treatment. For a comparison with the results of our study, we considered only reports fulfilling the following criteria: unselected IB1–IIB stage cervical cancer according to the 1994 International Federation of Gynecology and Obstetrics (FIGO) and 2009 FIGO staging systems, prospective design, more than 100 cases per assessment group, and median follow-up period of more than 3 years. According to that survey, 5-year overall survival for patients with unselected stage IB1, IB2, IIA1, and IIA2 cervical carcinomas treated with radical hysterectomy and adjuvant radiotherapy or chemoradiotherapy is about 85%. 48 (28%) grade 2 and 3 complications assessed with the Franco-Italian glossary were reported in 1997 for a cohort of 169 patients, of whom 108 (64%) received adjuvant radiotherapy. A retrospective analysis published in 2016 indicated similar morbidity for 243 patients with 83 (34%) instances of adjuvant radiotherapy. Optimal chemoradiotherapy of stage IIB cancer achieved 70% overall survival probability at 5 years. Periaortic lymph node metastases in cervical cancer are classified according to their location in the craniocaudal axis. Their surgical resection has a mainly diagnostic intent for radiotherapy planning. Periaortic lymph node metastases are generally considered as a poor prognostic factor associated with a 5-year survival probability of 10–25%, despite extended-field chemoradiotherapy.

Added value of this study

Total mesometrial resection and therapeutic lymph node dissection without adjuvant radiotherapy for stage IB1, IB2, IIA1, and IIA2 cervical cancer achieve outcomes that compare favourably with those of traditional surgery combined with postoperative chemoradiotherapy or radiotherapy. The results for stage IIB carcinomas treated by total or extended mesometrial resection correspond to those of state-of-the-art radiotherapy. This study also shows the prognostic value of ontogenetic local tumour staging and introduces a novel ontogenetic regional tumour staging system. Periaortic lymph node metastases represent a dual entity with different origin, topography, and prognosis.

Implications of all the available evidence

The long-term results from this large study cohort provide evidence to support the management of cervical cancer on the basis of the theory of ontogenetic cancer fields, applying ontogenetic local and regional staging, cancer field resection, and therapeutic lymph node dissection. The broad clinical application of this approach now needs to be tested in prospective multicentre trials.

chemoradiotherapy after radical surgery,[10] 4-year overall survival was 81% for 127 patients with stage IB1, IB2, IIA1, and IIA2 cancers with a median tumour diameter of 2·2 cm (range 0·6–5·2), and of whom 42 (33%) were pT2b, 110 (87%) were pN1, and five (4%) had positive resection margins. In another study[11] of 137 patients with stage IB1 or IB2 cervical carcinoma with intermediate risk factors comprising tumour size, stromal invasion, and lymphovascular space involvement, who were randomly assigned to postoperative pelvic irradiation after radical hysterectomy, 24 (18%) had recurrences and 21 (15%) died because of the disease or treatment-related morbidity. A randomised trial comparing minimally invasive surgery to open surgery for early stage cervical carcinoma reported 4·5-year recurrence-free survival of 96·5% (95% CI 92·7–98·4) in 312 patients in the open surgery group, including 287 (92%) of 312 patients with stage IB and 25 (8%) patients with stage IA1 or IA2 disease.[12] These patients underwent a two-stage selection process to exclude lymph node metastases (preoperatively and intraoperatively), and 37 (13%) of 282 were pN1 and 11 (6%) were pT2b. 73 (23%) of 312 patients received adjuvant radiotherapy with or without chemotherapy.

We have previously challenged the model of randomly diffusive local tumour spread for carcinoma of the cervix and vulva, and we have provided evidence that local propagation is determined by cancer fields anatomically defined by the mature tissue derivatives of the morphogenetic fields, which are involved in the stepwise development of the mature tissue from which the cancer originated.[13,14] Only within the cancer field of an individual tumour is its local spread stochastic and, therefore, occurs in all directions. However, crossing the border of the cancer field requires malignant progression, which is a stepwise process. Although the dynamics of malignant progression are not predictable, the sequence and the size of the associated cancer fields are fixed by morphogenesis, which has given rise to the concepts of ontogenetic staging and cancer field resection in oncology.

We have shown that ontogenetic local staging for cervical cancer is feasible and that the incorporation of

cancer field resection into various new procedures, such as total mesometrial resection (TMMR) supplemented by therapeutic lymph node dissection (tLND), without adjuvant radiotherapy, has the potential to improve treatment results compared with conventional principles and practice.[15,16] 5-year overall survival for 212 patients with 1994 FIGO stage IB1, IB2, IIA, and selected IIB cervical carcinoma was 96% (95% CI 93–99) and was 91% (81–100) for a subgroup of 44 (21%) patients with lymph node metastases.[16]

In this Article, we report the mature, long-term results of the Leipzig School Mesometrial Resection Study, in which we assessed the treatment of carcinoma of the uterine cervix with mesometrial resection without adjuvant radiotherapy. Additionally, we present results regarding the pattern of regional cervical cancer spread and their interpretation in light of the theory of ontogenetic cancer fields.

Methods

Study design and participants

We did a single-centre, prospective, observational, cohort study at the University of Leipzig (Leipzig, Germany), with the aim of investigating cancer field surgery for primary carcinoma of the uterine cervix without adjuvant radiotherapy. Participants were admitted to the Leipzig University Medical Center and surgically treated by the staff of the Leipzig School of Radical Pelvic Surgery under the supervision of MH. The full study protocol is included in the appendix (p 1).

See Online for appendix

Patients of any age with cervical carcinoma 2009 FIGO stages IB1, 1B2, IIA1, IIA2, or IIB without evidence of bladder wall involvement, as indicated by cystoscopic and MRI findings, were eligible. Patients with compromised general condition (Karnofsky index <80%, American Society of Anesthesiologists score ≥3), body-mass index (BMI) of more than 35 kg/m², previous pelvic radiotherapy or major pelvic surgery (except simple hysterectomy), and neuroendocrine cervical carcinomas were excluded. Laboratory tests done to assess eligibility were a complete blood count at baseline, electrolytes, total serum protein, albumin, liver enzymes (alanine and aspartate aminotransferases), total bilirubin, creatinine, urea, glucose, C-reactive protein, thyroid-stimulating hormone, urinary analysis, and coagulation status. Normal values for these tests were required for surgery. During the study period, the inclusion criteria were extended stepwise. Post-hysterectomy mesometrial resection for 2009 FIGO stage IB1 cervical cancer in patients who had simple hysterectomy was included from July 30, 2002. The development of extended mesometrial resection (EMMR) allowed the inclusion of patients with all FIGO IIB and selected cases of FIGO IIIB cancers without macroscopic evidence of bladder wall infiltration from June 22, 2006, onward. Until July 8, 2009, patients with tumour sizes exceeding 5 cm had preoperative downsizing chemotherapy with cisplatin.[15,16] Thereafter, neoadjuvant systemic treatment was abandoned and all FIGO IIB cervical cancers without evidence for bladder wall infiltration irrespective of tumour size were included in the mesometrial resection study. Restriction by BMI was raised to an upper limit of 40 kg/m² on May 3, 2005. Postoperative adjuvant chemotherapy with cisplatin, initially recommended only to patients with para-aortic lymph node metastases, was offered to patients with two or more pelvic lymph node metastases irrespective of extracapsular spread from Sept 1, 2005.[16]

All patients gave informed written consent to participate in the study. The study was approved by the Ethics Committee of the University of Leipzig (012/13-28012013; 171-2006; 192/2001; 151/2000).

Procedures

All tumours were preoperatively assessed according to the FIGO staging criteria.[17] Initially, the 1994 FIGO staging system was used. Following their publication, the 2009 FIGO criteria were applied and previous stages adjusted for evaluation. Because the 2018 FIGO staging system is based on different diagnostic tools, the retrospective adaptation of the prospectively assessed FIGO stages was not possible.[18]

Surgical treatment was based on clinical ontogenetic staging obtained from the examination under anaesthesia with the patient's pelvic MRI scans available in the operating room. MRI findings were used to plan the surgery (extent of laparotomy and selection of surgical instruments), but not to exclude patients with cervical cancer from surgical treatment. The surgical procedures, TMMR, EMMR, and tLND, open techniques done abdominally or abdominoperineally, have been described previously.[15,19,20] A summary of the techniques with surgical amendments (TMMR 3.0) is given in the appendix (p 2). TMMR excises the complete Müllerian compartment, except the distal vagina, and the vascular and ligamentous mesometria. EMMR additionally removes any of the following tissues: bladder adventitia, mesentery, wall, distal ureter, and distal vagina. tLND harvests the first-line, second-line, and third-line lymph node regions of cervical cancer. TMMR 3.0 is demonstrated in an updated video in a previous publication.[15] The type of surgery chosen for each patient was directed by the ontogenetic tumour and nodal stage as determined preoperatively and intraoperatively. Details are provided in the appendix (pp 15–16). Histopathological assessment of resected specimens was done as previously described (appendix p 3).[13,16] Early and late treatment-related morbidity was evaluated according to the Franco-Italian glossary.[21] This validated instrument scores cutaneous, gastrointestinal, neuronal, respiratory, urinary, and vascular morbidity with four grades each. Lymph oedema was assessed, as previously reported, according to the recommendations of the International Society of Lymphology and the European Center for Lymphology (Földi Klinik, Hinterzarten, Germany).[16]

Patients were followed up regularly for 5 years and on a volunteer basis thereafter. Assessment of disease state, treatment-related morbidity, and survival was done at 3-month intervals for the first 2 years after surgery, and every 6 months thereafter. The disease course of patients who did not attend the regular aftercare programme at the University of Leipzig was obtained from the patients or their gynaecologists and family doctors in regular surveys. Tumour relapses were classified as pelvic, distant, or both, according to the information available from the hospitals or institutions treating the patients with recurrent disease. Pelvic and solitary distant relapses had to be confirmed by histology. Multiple distant relapses were ascertained from diagnostic imaging. Interim survival analyses were done yearly.

Primary outcomes for the study were disease-specific survival, recurrence-free survival, and treatment-related morbidity. Secondary outcomes were histopathological assessments, the analysis of relapse pattern with regard to ontogenetic anatomy, and overall survival.

Statistical analysis

The recruitment goal was initially set at 100 patients (Oct 16, 1999), then 200 after successful establishment of the procedures (Oct 9, 2005), followed by 500 when further surgical amendments were made (June 1, 2009). These numbers and the stepwise approach were chosen for historical reasons. The first scientific report[22] on radical hysterectomy as developed by Wertheim presented the outcome of 500 patients.

For statistical analysis, data were imported from Microsoft Excel (2016) into R (version 3.5.0). The two-tailed significance level was defined as 0·05 in general. Baseline categorical characteristics are reported in absolute numbers and percentages. Medians with IQR and means with SD are given for quantitative data. Disease-specific, recurrence-free, and overall survival were calculated on the basis of the time between the day of surgery and the diagnosis of a histologically confirmed relapse, death from disease, death from any cause, or loss to follow-up. All deaths from unknown cause were counted as disease-specific. The median follow-up time was defined as the median time from study inclusion to censoring in patients who were alive at the last follow-up. For survival analysis, Kaplan-Meier curves were drawn using the survival package for R (version 2.41.3). Variance was calculated using the Greenwood formula as implemented in the survival package. Cox proportional hazards regression modelling was used to assess the effect of pathological and ontogenetic staging on disease-specific survival. These models for local and regional tumour spread also included age, third root of tumour size, and grading. Hazard ratios with 95% CIs are shown by forest plots. Statistical analyses were done in R (version 3.5.0). This trial is registered with the German Clinical Trials Register, number DRKS00015171.

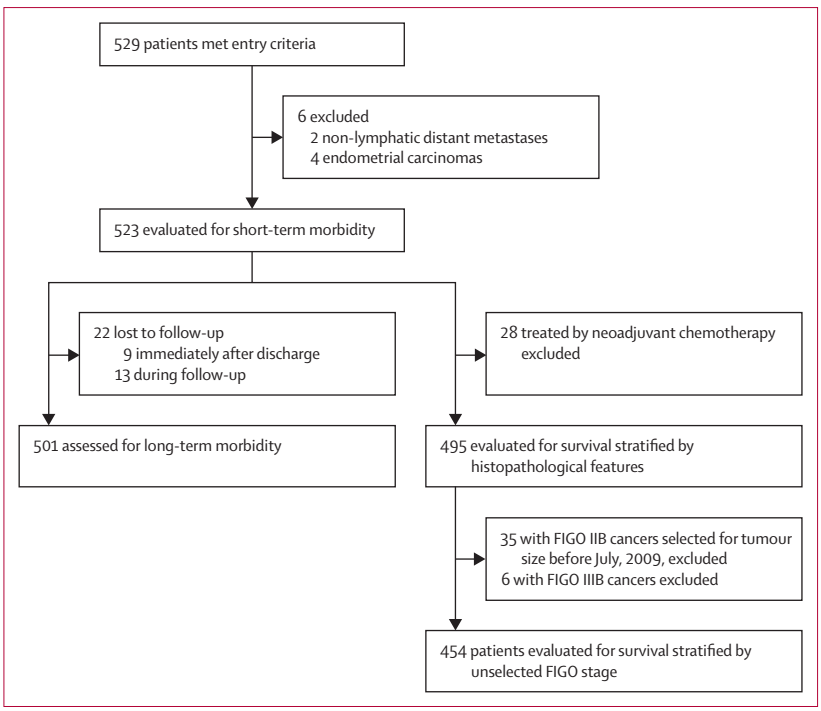

Figure 1: **Study profile**
FIGO=International Federation of Gynecology and Obstetrics.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

529 patients who had surgery between Oct 16, 1999, and June 27, 2017, met inclusion criteria and were included in the study. After six patients were excluded because of distant metastasis or the presence of endometrial cancers, 523 patients were evaluated for short-term morbidity (figure 1). Patient and pretreatment tumour characteristics of the study cohort are given in table 1. To avoid pretreatment or selection bias, of the 523 patients, 28 (5%) patients who received neoadjuvant chemotherapy were excluded from the histopathological analysis, and 35 (7%) with FIGO IIB cancers treated before July 2009 and six (1%) with FIGO IIIB cancers were excluded from the survival analysis (figure 1). Post-hysterectomy mesometrial resections were done in five (1%) patients with pT1b cervical carcinoma inadequately treated with simple hysterectomy. Three (< 1%) gravid patients of 8, 11, and 20 gestational weeks received surgery with the conceptus in situ. Three pregnant patients had a caesarean section immediately before TMMR after 29, 34, or 38 weeks of gestation. 501 (96%) of the 523 patients were assessed for long-term morbidity after nine (2%) had been lost to follow-up immediately

	Patients (n=523)
Age, years	
Mean (SD)	46 (12)
Median (IQR)	44 (37–54)
Body-mass index, kg/m²	
Mean (SD)	24·5 (4·5)
Median (IQR)	23 (23–27)
Previous uterine surgery	
Conisation	185 (35%)
Caesarean section	31 (6%)
Simple hysterectomy	5 (1%)
Supracervical hysterectomy	4 (1%)
Gravid uterus	6 (1%)
Histological type	
Squamous cell carcinoma	395 (76%)
Adenocarcinoma	104 (20%)
Adenosquamous carcinoma	24 (5%)
FIGO stage	
IB1	273 (52%)
IB2	55 (11%)
IIA1	20 (4%)
IIA2	9 (2%)
IIB	160 (31%)
IIIB	6 (1%)
Neoadjuvant chemotherapy	28 (5%)
Surgical access	
Abdominal	510 (98%)
Abdominoperineal	13 (2%)
Mesometrial resection type	
Total mesometrial resection	467 (89%)
Extended mesometrial resection	56 (11%)
Tissues types in extended mesometrial resection specimens	
Bladder adventitia with or without mesotissue	36/56 (64%)
Bladder wall	17/56 (30%)
Distal ureter with or without mesureter	21/56 (38%)
Sinus vagina with or without vestibulum vulvae	4/56 (7%)
Mesorectum with or without rectum	4/56 (7%)
Therapeutic lymph node dissection type	
Pelvic first-line	523 (100%)
Pelvic first-line plus second-line	488 (93%)
Pelvic first-line plus aortic bifurcation	162 (31%)
Pelvic first-line plus perimesenteric periaortic	132 (25%)
Pelvic first-line plus periaortic infrarenal	70 (13%)

Data are n (%) or n/N (%), unless otherwise specified. FIGO=International Federation of Gynecology and Obstetrics.

Table 1: **Baseline patient and tumour characteristics**

after discharge and 13 (2%) did not complete their 5-year follow-up assessment. The clinical and pathological stages of these 22 patients lost to long-term follow-up are in the appendix (p 4). 112 (21%) of the 523 patients remain in the aftercare phase, as of Aug 15, 2018.

Histopathological results are shown in table 2. A mean of 45 (SD 12) and a median of 44 (IQR 37–52) lymph nodes were harvested by therapeutic lymph node dissection for the pelvic basins, nine (SD 4) and eight (IQR 6–11) for the aortic bifurcation subregion, nine (SD 4) and nine (IQR 7–12) for the perimesenteric subregion and 11 (SD 6) and ten (IQR 8–13) for the infrarenal periaortic subregions.

112 (21%) of 523 patients who received TMMR or EMMR had grade 2 (moderate) complications and 15 (3%) had grade 3 (severe) complications (table 3). One patient (<1%), who received TMMR, died from postoperative brain infarction. The most common moderate and severe treatment-related complications and sequelae were wound dehiscence (17 [3%]), hydronephrosis (17 [3%]), bowel obstruction (26 [5%]), and lymph oedema (33 [6%]; table 3). Laparotomy and ureter complications were more frequent with EMMR than with TMMR (table 3). Bowel obstruction occurred with equal frequency in patients treated with either TMMR or EMMR. Grade 2 leg oedema occurred in 24 (7%) of 362 patients who had pelvic lymph node dissection and in nine (5%) of 180 patients treated with pelvic and periaortic lymph node dissection. Treatment-related morbidity for the subgroup of 357 patients with 2009 FIGO stage IB1, IB2, IIA1, and IIA2 disease is shown in the appendix (p 4).

The median length of the post-treatment observation period was 61·8 months (IQR 49·3–94·8). 5-year disease-specific survival for the 495 patients with cervical cancer treated with cancer field surgery, including 159 (32%) pN1 cases and 148 (30%) pT2b cases, was 89·4% (95% CI 86·5–92·4), recurrence-free survival was 83·1% (95% CI 79·7–86·6), and overall survival was 87·9% (95% CI 84·8–91·1; appendix p 9). Kaplan-Meier curves of disease-specific survival for cancer of the uterine cervix treated with TMMR or EMMR and tLND stratified for 2009 FIGO stages are shown in figure 2A. 5-year disease-specific, recurrence-free, and overall survival estimates for subgroups defined by clinical and histopathological assessments are shown in the appendix (p 6).

The frequency of local spread of cervical cancer into developmentally defined tissues (cancer fields) inversely correlated with ontogenetic staging. 495 (100%) of 495 tumours had infiltrated the cervical stroma, the cancer field of stage oT1. The cervical adventitia stage oT2 cancer field was infiltrated in 149 (30%) patients, the uterine corpus in 109 (22%), and the Müllerian vagina in 55 (11%). Stage oT3a cancer fields were infiltrated as follows: mesometrium in 74 (15%) of 495 tumours, bladder adventitia and mesostructures in 30 (6%), and allantois bladder muscle in four (<1%). The frequency of tumour infiltration in stage oT3b or 4 cancer fields was two (<1%) in the mesorectum and two (<1%) in the mesureter. One patient (<1%) with an adenoid basal cell carcinoma of the cervix had an ovarian metastasis at the time of surgical treatment. In two patients (<1%), infiltrates of cervical squamous cell carcinoma were detected in the mesovarium and the infundibulopelvic ligament. Tumour involvement

	Patients (n=495)
Local spread	
Tumour size, mm	
Mean (SD)	33·1 (17·4)
Median (IQR)	31 (19–45)
Pathological T stages	
pT1b1	266 (54%)
PT1b2	59 (12%)
pT2a1	17 (3%)
pT2a2	5 (1%)
pT2b	148 (30%)
L stages	
L0	153 (31%)
L1	336 (68%)
Lx	6 (1%)
V stages	
V0	433 (87%)
V1	56 (11%)
Vx	6 (1%)
G stages	
G1	72 (15%)
G2	249 (50%)
G3	168 (34%)
Gx	6 (1%)
R stages	
R0	491 (99%)
R1	4 (1%)
Infiltration of cervical stroma	
1/3	116 (23%)
2/3	113 (23%)
3/3	265 (54%)
Not reported	1 (<1%)
Infiltrated extracervical tissues	
Uterine isthmus	111 (22%)
Uterine corpus	95 (19%)
Müllerian vagina*	55 (11%)
Paracervix	148 (30%)
Mesometrium	74 (15%)
Bladder adventitia with or without mesotissue	29 (6%)
Bladder muscle (allantois)	4 (1%)
Bladder muscle (urogenital sinus)	1 (<1%)
Ureter	1 (<1%)
Mesureter	2 (<1%)
Genital peritoneum	3 (<1%)
Bladder peritoneum	1 (<1%)
Umbilical artery	2 (<1%)
Sinus vagina	1 (<1%)
Vulva	1 (<1%)
Ovary	1 (<1%)

(Table 2 continues in next column)

(Continued from previous column)

	Patients (n=495)
Ontogenetic T stages	
oT1	299 (60%)
oT2	114 (23%)
oT3a	71 (14%)
oT3b	8 (2%)
oT4	3 (<1%)
Regional spread	
pN0†	345 (70%)
pN1‡	150 (30%)
Sentinel (one metastasis only)	49/150 (33%)
External iliac left	12/150 (8%)
External iliac right	5/150 (3%)
Paravisceral left	10/150 (7%)
Paravisceral right	11/150 (7%)
Mesometrial left	5/150 (3%)
Mesometrial right	6/150 (4%)
Pelvic first-line	150/150 (100%)
Second-line	42/150 (28%)
Aortic bifurcation	26/150 (17%)
Perimesenteric periaortic	25/150 (17%)
Infrarenal periaortic	18/150 (12%)
Periaortic first-line	6/150 (4%)
Third-line	25/150 (17%)
Extracapsular spread	43/150 (29%)
Number of lymph node metastases per patient	
Sentinel	1
First-line only	
Mean (SD)	2 (2)
Median (IQR)	2 (1–3)
First-line and second-line	
First-line	
Mean (SD)	4 (3)
Median (IQR)	4 (2–5)
Second-line	
Mean (SD)	2 (3)
Median (IQR)	1 (1–2)
First-line, second-line, and third-line	
First-line	
Mean (SD)	7 (4)
Median (IQR)	6 (4–10)
Second-line	
Mean (SD)	8 (8)
Median (IQR)	4 (3–12)
Third-line	
Mean (SD)	9 (9)
Median (IQR)	7 (1–15)

Data are n (%) or n/N (%), unless otherwise specified. *The human vagina has a dual ontogenesis. The proximal part is derived from the Müllerian system and the distal part from the urogenital sinus. †19 patients pretreated with neoadjuvant chemotherapy excluded. ‡Nine patients pretreated with neoadjuvant chemotherapy excluded.

Table 2: **Histopathological tumour characteristics**

	Total mesometrial resection and therapeutic lymph node dissection, n=467*				Extended mesometrial resection and therapeutic lymph node dissection, n=56†			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous	18 (4%)	14 (3%)	1 (<1%)	..	3 (5%)	6 (11%)	..	..
Wound infection or dehiscence (conservative treatment)	18 (4%)	..	..	..	3 (5%)	..	..	..
Wound dehiscence (surgical treatment)	..	10 (2%)	..	..	..	6 (11%)	..	..
Wound dehiscence (necrotising fasciitis)	..	..	1 (<1%)	..	..	..	..	..
Abdominal hernia	..	2 (<1%)	..	..	..	..	..	..
Keloid	..	2 (<1%)	..	..	..	..	..	..
Gastrointestinal	12 (3%)	23 (5%)	..	..	..	3 (5%)	..	..
Bowel obstruction (conservative treatment)	12 (3%)	..	..	..	..	..	..	..
Bowel obstruction (surgical treatment)	..	23 (5%)	..	..	..	3 (5%)	..	..
Neuronal	7 (1%)	2 (<1%)	..	..	4 (7%)	..	..	..
Paresis, short-term	4 (<1%)	..	..	..	2 (4%)	..	..	..
Paresis, long-term	..	2 (<1%)	..	..	..	..	..	..
Dysesthesia	2 (<1%)	..	..	..	2 (4%)	..	..	..
Epileptic seizure	1 (<1%)	..	..	..	..	..	..	..
Respiratory	3 (<1%)	8 (2%)	..	..	1 (2%)	3 (5%)	..	..
Pneumonia	2 (<1%)	..	..	..	1 (2%)	..	..	..
Pleural effusion	1 (<1%)	..	..	..	..	..	..	..
Embolism	..	8 (2%)	..	..	..	3 (5%)	..	..
Urinary	72 (15%)	15 (3%)	8 (2%)	..	13 (23%)	4 (7%)	6 (11%)	..
Infection	12 (3%)	..	..	..	..	..	..	..
Retention, temporary	38 (8%)	..	..	..	11 (20%)	..	..	..
Retention, permanent	..	1 (<1%)	..	..	..	..	..	..
Stress incontinence grade I	14 (3%)	..	..	..	1 (2%)	..	..	..
Stress incontinence grade II	..	..	..	..	..	1 (2%)	..	..
Hydronephrosis, observation	8 (2%)	..	..	..	1 (2%)	..	..	..
Hydronephrosis, stented	..	14 (3%)	..	..	..	2 (4%)	..	..
Hydronephrosis, loss of kidney	..	..	..	..	..	..	1 (2%)	..
Ureteral necrosis	..	..	5 (1%)	..	..	..	3 (5%)	..
Vesicovaginal fistula (spontaneous closure)	..	..	..	..	..	1 (2%)	..	..
Vesicovaginal or ureterovaginal fistula (surgical treatment)	..	..	3 (<1%)	..	..	..	2 (4%)	..
Vascular	58 (12%)	33 (7%)	..	1 (<1%)	3 (5%)	4 (7%)	..	..
Postoperative bleeding (no intervention)	3 (<1%)	..	..	..	..	..	..	..
Postoperative bleeding (surgical revision)	..	1 (<1%)	..	..	..	..	..	..
Thrombosis	5 (1%)	..	..	..	..	..	..	..
Lymphoedema, grade I	38 (8%)	..	..	..	2 (4%)	..	..	..
Lymphoedema, grade II	..	30 (6%)	..	..	..	3 (5%)	..	..
Lymphocyst, no symptoms	8 (2%)	..	..	..	..	..	..	..
Lymphocyst, infected	..	2 (<1%)	..	..	..	1 (2%)	..	..
Lymphascos	4 (<1%)	..	..	..	1 (2%)	..	..	..
Brain infarction	..	..	..	1 (<1%)	..	..	..	..

Dara are n (%). *269 (58%) patients had no complications or sequelae (except loss of fertility and abdominal scar). †18 (32%) patients had no complications or sequelae (except loss of fertility and abdominal scar).

Table 3: **Complications and sequelae according to the Franco-Italian glossary[21]**

of the uterine corpus was present in all three (1%) patients. Disease-specific survival estimates stratified for pT and oT stages of cervical cancer are shown in figure 2B and 2C.

Topographical mapping of regional tumour spread on the basis of the results of 150 (30%) of 495 patients with lymph node metastases defines regional cancer fields (table 2). The external iliac and paravisceral basin nodes and the mesometrial lymph nodes were confirmed as pelvic first-line nodes for cervical cancer, because single lymph node metastases were observed in these nodes. In all instances of metastatic involvement of second-line nodes located in the common iliac and presacral basins,

first-line nodes contained metastases. Further downstream, the lymph node metastasis pattern becomes more complex. Periaortic lymph node metastases were subdivided along the caudocranial axis into aortic bifurcation, perimesenteric, and infrarenal locations (figure 3A). 24 (92%) of 26 patients with aortic bifurcation metastases had second-line metastases. However, five (45%) of 11 patients with cervical cancers with perimesenteric metastases as the metastatic front had no aortic bifurcation and no pelvic second-line metastases, but all had pelvic first-line metastases. All patients (18 [12%] of 150) with infrarenal metastases also had upstream metastases in the lower periaortic region. The regional cancer fields of cervical carcinoma are illustrated in figure 3B. The number of lymph node metastases increased in lymph nodes downstream of sentinel nodes (table 2). Whereas survival decreased stepwise if the front of regional spread progressed from first-line to aortic bifurcation lymph node subregions, metastases that developed further downstream in the perimesenteric aortic basin were associated with substantially better outcome; however, this was not statistically compared, but is clearly shown by the curves (appendix p 10). In eight (89%) of nine patients with perimesenteric lymph node metastases, cervical cancer infiltrated the uterine corpus or isthmus. Periaortic lymph node metastases without metastatic occupation of pelvic second-line lymph node regions and infiltration of the uterine isthmus or corpus prognostically equated to pelvic first-line metastases. Metastases in the infrarenal periaortic lymph node basin, the furthest downstream region to be cleared by therapeutic lymph node dissection, indicated the worst prognosis, as shown by survival curves (appendix p 10). Periaortic metastases that have developed in addition to second-line metastases represent third-line metastases. A single metastasis and multiple metastases in the first-line, second-line, and third-line regions define an ontogenetic nodal staging system (oN1s and oN1, 2, and 3). Survival curves stratified for pathological and ontogenetic nodal staging are in the appendix (p 11).

The proportions of metastases spreading beyond the lymph node capsule into the perinodal fatty tissue was two (4%) of 49 sentinel nodes, 37 (25%) of 150 first-line nodes, 19 (45%) of 42 second-line nodes, and nine (36%) of 25 third-line nodes. Extracapsular spread substantially worsened patients' survival (appendix p 11). The extracapsular spread effects persisted, but the difference between the groups was smaller if analysed separately for sentinel and first-line, second-line, and third-line metastases (appendix p 12).

The type of recurrence—in the pelvis only, simultaneously in the pelvis and at distant sites, or at distant sites only—was associated with the ontogenetic tumour stage, the pathological and ontogenetic nodal stage, and the presence of extracapsular spread of the lymph node metastases. Relapses diagnosed in the pelvis were more frequent than at distant sites in patients

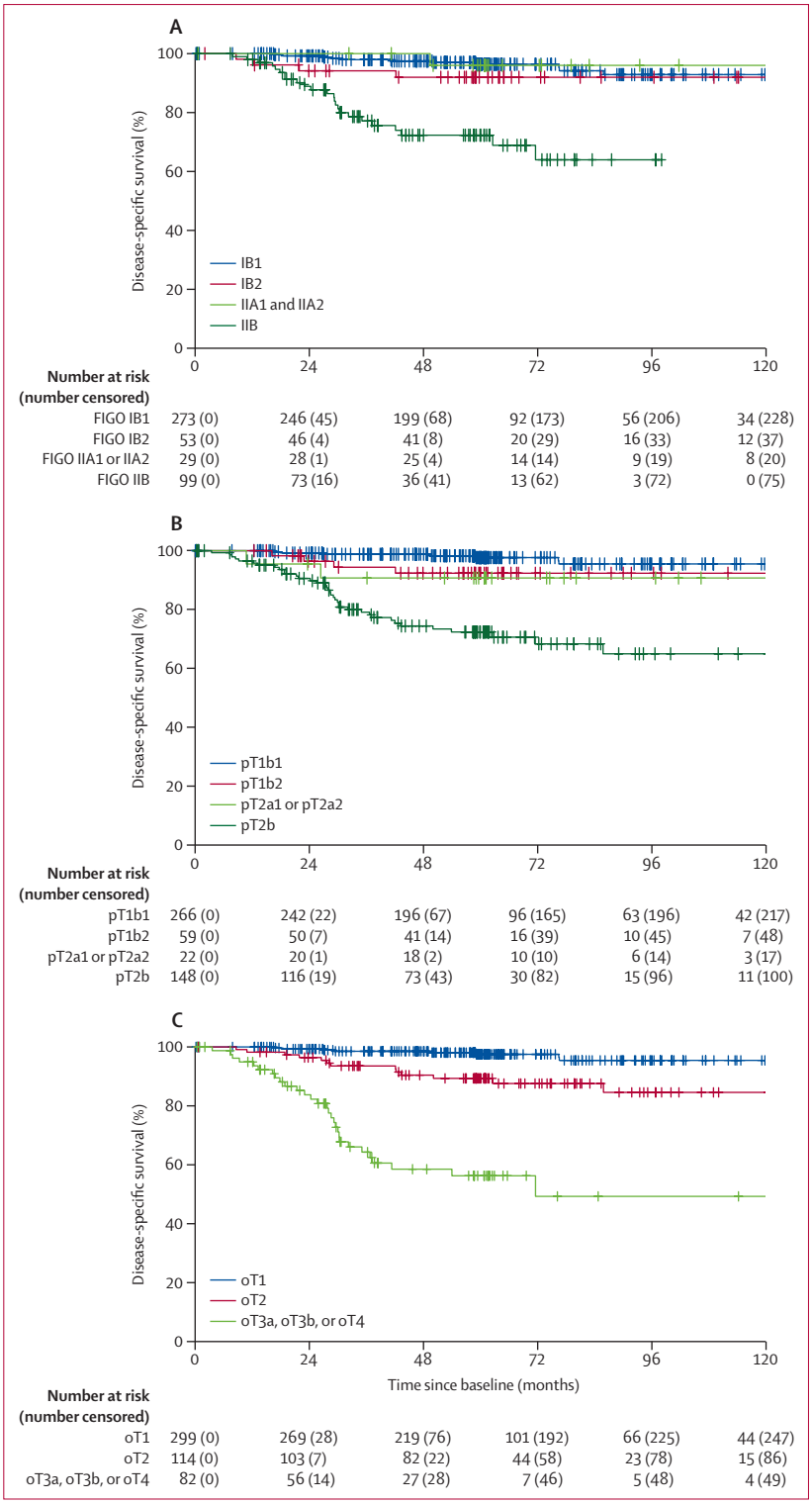

Figure 2: **Kaplan-Meier estimates for disease-specific survival of patients with cervical cancer treated with total or extended mesometrial resection and therapeutic lymph node dissection.**
(A) Stratified for FIGO stage. (B) Stratified for pT stage. (C) Stratified for oT stage. 28 patients pretreated with neoadjuvant chemotherapy were excluded. Only FIGO stage IIB cases without size restriction treated from July, 2009, onwards are included in panel A. FIGO=International Federation of Gynecology and Obstetrics.

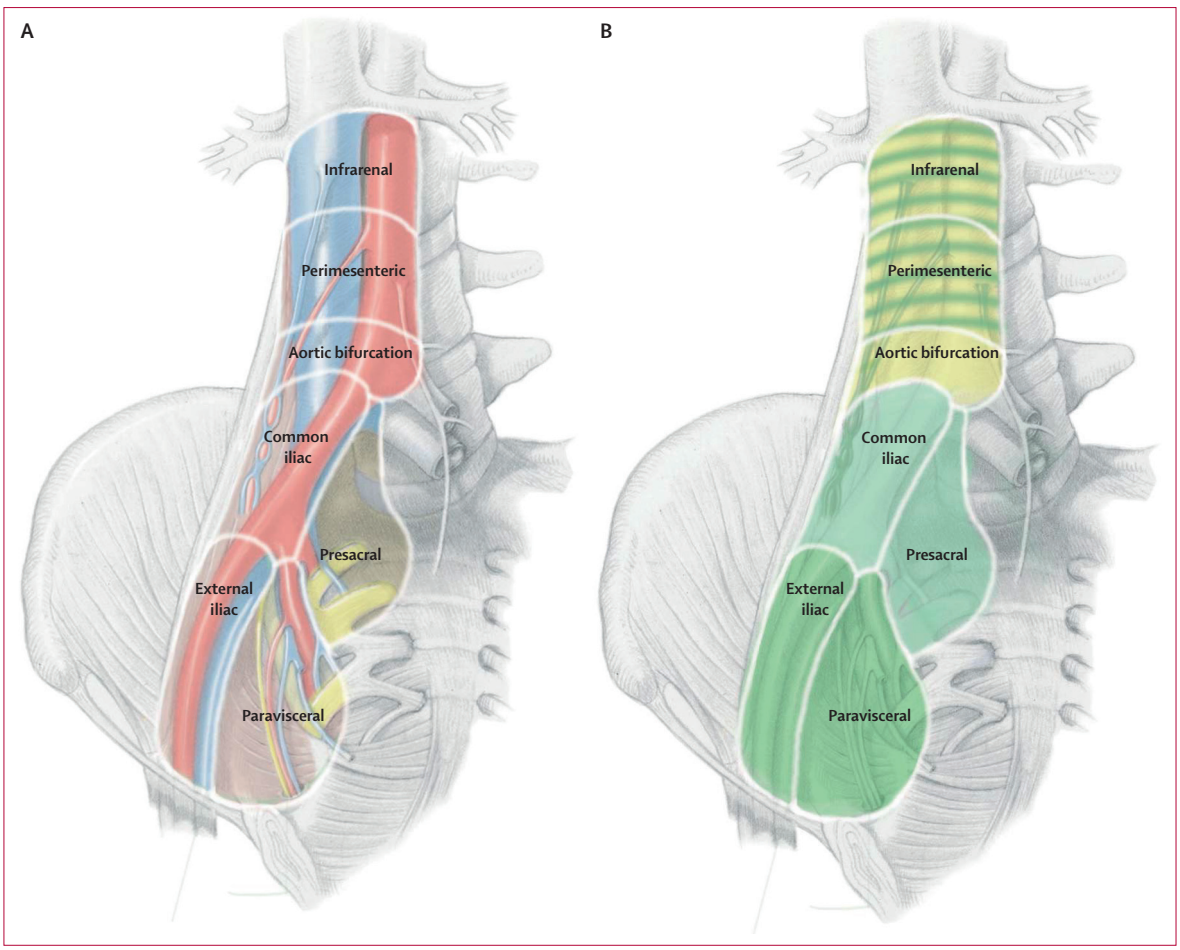

Figure 3: **Regional cancer fields of cervical carcinoma**
(A) Topographical anatomy of parietal lymph node regions for regional cervical cancer spread. The right pelvic and lumbar retroperitoneum is shown from the ventral perspective. The lymphatic tissue is not depicted in the drawing to clarify the lymph node regions with regard to the neurovascular landmarks. (B) The lymph node regions, topographically defined in panel A, are colour-coded to represent their involvement in stepwise metastasis of cervical carcinoma. Green represents first-line nodes directly connected to the uterine cervix, light green represents second-line nodes necessitating the presence of metastases in first-line nodes, and yellow represents third-line nodes necessitating the presence of metastases in second-line nodes. Note that the periaortic subregion, except for the aortic bifurcation, might harbour both first-line and third-line nodes.

whose primary cancers exhibited oT1 and oT2, oN1s to oN2 stages, and no evidence of extracapsular spread (appendix p 13). Advanced oT and oN stage and the presence of extracapsular spread were associated with recurrence at distant sites (appendix p 13).

The results of Cox proportional hazards analysis of multiple variables on disease-specific survival are shown in the appendix (pp 7–8, 14). oT stage (HR 17·5, 95% CI 3·80–80·7; p<0·0001 for oT3b or oT4) and tumour size (2·02, 1·03–3·97; p=0·04) were significantly associated with local tumour spread, and oN stage (2·94, 1·05–8·25; p=0·036), extracapsular spread (2·24, 1·10–4·57; 0·023), and tumour size (2·66, 1·24–5·71; p=0·010) were significantly associated with regional spread.

Discussion

The results of this study confirm those from our previous reports[13,15] on TMMR for patients with 2009 FIGO stage IB1, IB2, IIA1, or IIA2 cervical carcinoma in a larger patient cohort and with longer follow-up. Inclusion of FIGO stage IIB cervical carcinomas without size restriction, owing to the development of EMMR, enabled us to present the oncological results for tumours of all unselected FIGO stages from IB1 to IIB and for all subgroups defined by histopathological features. Although no substitute for a randomised trial, the oncological results of our prospective study of cancer field surgery without adjuvant radiotherapy compare favourably with those of traditional surgery and adjuvant chemoradiotherapy, in the case of histopathological risk factors, and with primary chemoradiotherapy.[8–12,23] The most common moderate treatment-related complications and sequelae were wound dehiscence, hydronephrosis, bowel obstruction, and lymph oedema, with laparotomy and ureter complications occuring more frequently with EMMR

than with TMMR. The extension of therapeutic lymph node dissection had no detectable effect on the incidence of lymph oedema. Using the same instruments to assess treatment-related morbidity[21] allowed for preliminary comparisons with conventional treatment by radical surgery with adjuvant radiotherapy. Grade 2 or 3 complications, according to the Franco-Italian glossary, occurred in 28% of patients treated for 2009 FIGO stage IB1, IB2, IIA1, and IIA2 cervical cancer with conventional therapy[8,24] and 19% with cancer field surgery. This cross-study comparison must be interpreted cautiously, because its validity is limited by the absence of randomisation and the fact that studies were done at different times with unknown confounders.

The results of therapeutic lymph node dissection without postoperative radiotherapy confirmed the subregions and frequency of pelvic first-line and second-line lymph node metastases reported previously[19] and are consistent with investigations of the lymphatic drainage of the cervix uteri.[25,26] Additionally, we show lymph node metastases occupying periaortic subregions, which, to our knowledge, has not previously been reported. We found a different prognostic value for periaortic lymph node metastases on the basis of whether second-line basins contained metastases or not. All patients whose basins did not contain second-line metastases had local tumour infiltration of the uterine corpus or at least of the isthmus. Survival of these patients did not seem to differ from that of patients with first-line lymph node metastases in the pelvis, whereas periaortic lymph node metastases in the presence of second-line metastases was associated with worse prognosis.

These results can be explained by the ontogenetic anatomy of the lymphatic system as briefly outlined in the appendix (p 3). Unlike the current practice in gynaecologic oncology of adhering to guidelines,[6] which does not discriminate between first-line and third-line periaortic metastases, cancer field surgery adapts management to the individual disease states (appendix pp 15–16).

This study also emphasises the importance of extracapsular spread as an indicator of a dismal prognosis as previously reported, but not widely applied.[27] The clinical and histopathological results of this study further support the ontogenetic cancer field theory.[28,29] We have provided evidence for the regional spread of cervical carcinoma, as previously provided for patterns of local spread, if one assumes that the presentation of topobiological information within a lymph node is related to its territory of immunological surveillance.[30] Cervical cancer cells must advance to higher ontogenetic stages to spread to second-line and third-line lymph nodes. Extracapsular spread of cervical carcinoma necessitates malignant progression to stage oT4. Both second-line or third-line lymph node metastases and extracapsular spread, therefore, indicate the ability of cervical cancer cells to colonise many intrapelvic and extrapelvic tissues. The new concept of staging based on ontogenetic anatomy both for local and regional tumor spread should more accurately represent the malignant progression of the indivdual cancer and, therefore, the prognosis for the patient than the pTN system, which is derived empirically. We have previously shown the effectiveness of ontogenetic staging for vulva carcinoma as well.[14]

Our study had some limitations. Preoperative investigation would have been necessary for a more accurate evaluation of treatment-related lymph oedema. Our study did not include assessment of quality of life with validated instruments. However, because moderate and severe treatment-related complications are less frequent with cancer field surgery than as reported for traditional treatment, post-therapy quality of life should have been increased too. We are also aware of the methodological limitations of a single-centre, uncontrolled study. Although selection bias can be excluded because patients with cervical carcinoma 2009 FIGO stages IB1, IB2, IIA1, IIA2, and IIB (without the rare cases of bladder wall infiltration) have been evaluated in our study, possible variations in outcome between different centres and surgeons could not be addressed. Nevertheless, the conventional treatment of cervical carcinoma is based on inappropriate views on local and regional tumor spread and imprecise surgical anatomy derived from dissection artifacts.The successful outcome of our study might encourage multicentre randomised trials that compare cancer field surgery, as specified in the TMMR or EMMR plus tLND management procedure, with conventional surgery and radiotherapy for carcinoma of the uterine cervix 2009 FIGO stages IB1, IB2, IIA1, IIA2, and IIB. However, confirmatory clinical results from other centres are prerequisite for such trials. Controlled multicentre studies of cancer field surgery for cervical cancer are already underway (eg, NCT01819077).

Contributors

MH developed the theory of ontogenetic cancer fields and its clinical translation into ontogenetic tumour and nodal staging as well as surgery for cervical carcinoma. He was the principal investigator of the Leipzig study, analysed and interpreted data, designed figures, and wrote the manuscript. BW collected, processed, and interpreted data, did the stratified analysis, designed figures, and wrote the manuscript. KS retrieved the follow-up data. MM reviewed the statistical analysis and added further calculations. BA, RK, and ND contributed to the literature search, data analysis, and data interpretation. L-CH did or supervised the histopathological investigations.

Declaration of interests

BA reports personal fees from Pfizer, Novartis Pharma, AstraZeneca, Amgen, and Roche Pharma outside the submitted work. RK reports personal fees and travelling support from Intuitive Surgical Inc, Medtronic, and Cambridge Medical Robotics outside the submitted work. All other authors declare no competing interests.

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