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ScienceDirect
Gynecologic Oncology 108 (2008) 63–67
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Extracapsular extension of pelvic lymph node metastases is of prognostic value in carcinoma of the cervix uteri

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Received 21 June 2007
Available online 24 October 2007

Abstract

Objectives. Pelvic lymph node involvement is a well-recognized prognostic factor in cervical carcinoma (CX). Limited knowledge exists about extranodal extension of the tumor outside the lymph node capsule, i.e. extracapsular spread (ECS).

Methods. Two hundred fifty-six cases of surgically treated CX (FIGO stage IB1 to IIB) with pelvic lymph node involvement were evaluated regarding the occurrence of extranodal spread of the metastatic deposits outside the lymph node capsule (ECS), determined on standardized handled lymphadenectomy specimens, regarding their impact of recurrent disease and overall survival during a median follow-up time of 62 months (95% CI 51–73 months).

Results. ECS was seen in 30.9% (79/256) of the cases. The occurrence of ECS showed a significant correlation to advanced stage disease ($p=0.02$), the number of involved nodes ($p<0.001$) and the size of metastatic deposits ($p<0.01$). The 5-year recurrence-free survival rate in patients with ECS was significant lower compared to patients without ECS (59.7% [95% CI: 46.3%–73.2%] versus 67.2% [95% CI: 58.9%–75.5%]; ($p=0.04$).

The 5-year overall survival rate was significant lower in patients with ECS (33.5% [95% CI: 20.6%–46.3%] vs. 60.5% [95% CI: 52.3%–68.6%]; $p<0.001$). In multivariate analysis, tumor stage, number of involved pelvic nodes, tumor differentiation and ECS were independent prognostic factors.

Conclusions. The results indicate that extracapsular spread (ECS) of pelvic lymph node metastases is of prognostic impact in cervical carcinomas. A revised FIGO/TNM classification system for pelvic lymph node disease is recommended: ECS 0=lymph node involvement without extranodal spread of the metastatic deposits and ECS 1=lymph node involvement with extranodal spread of the metastatic deposits.

Keywords: Cervical carcinoma; Pelvic lymph nodes; Metastases; Metastatic disease; Extracapsular spread

Introduction

Studies overwhelming indicate that the presence of lymph node metastases is an independent prognostic factor for overall and disease-specific survival, local recurrence and disease-free interval in carcinoma of the cervix uteri (CX; [1]). Other parameters related to lymph node status are also mentioned in the literature as prognostic factors. These parameters include the number of metastatic involved nodes, the size of the metastatic deposits and the localization of the metastatic nodes in the pelvis [2–4].

Previous studies of non-gynecological carcinomas as well as in those patients affected by breast or vulvar cancer have been shown that extranodal extension of the tumor outside the lymph node capsule, i.e. extracapsular spread (ECS), is another significant predictor of adverse outcome in node-positive patients [5–9]. But, there are only limited number of studies dealing with ECS in patients with CX, covering a small number of patients with inconsistent results [4,10–12].

The aim of the present study was to determine the prognostic impact of ECS in patients with surgically treated cervical carcinoma.

Materials and methods

Data from patients with CX and histologically confirmed pelvic lymph node involvement, staged FIGO IB to IIB were obtained from the files of our so-called

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doi:10.1016/j.ygyno.2007.08.086

Table 1
Patients characteristics

Median age	42 years (range 23–74 years)
Stage distribution	
pT1b	101 (39.5%)
pT2	142 (55.5%)
Unknown	13 (5.1%)
Tumor type	
Squamous cell carcinoma	243 (94.9%)
Adenocarcinoma	13 (5.1%)
Lymphovascular space involvement	
No	47 (18.4%)
Yes	209 (81.6%)
Tumor grade	
G1	100 (39.1%)
G2	88 (34.4%)
G3	68 (26.5%)
Laterality of pelvic lymph node involvement	
Unilateral	151 (59.0%)
Bilateral	104 (40.6%)
Unknown	1 (0.4%)
Extracapsular spread in nodal-positive cases	
No	177 (69.1%)
Yes	79 (30.9%)
Number of involved pelvic nodes	
<3	193 (75.4%)
>3	63 (24.6%)
Size of metastatic deposits in pelvic lymph nodes	
<5 mm	115 (44.9%)
>5 mm	140 (54.7%)
Unknown	1 (0.4%)
Recurrent disease	
No	175 (68.4%)
Yes	72 (28.1%)
Unknown	9 (3.5%)

Wertheim-Archive [13]. Patients who received neoadjuvant therapy, those with incomplete local tumor resection (R1- or R2-resection) and tumors of other histologic type as squamous cell and adenocarcinomas of the cervix uteri were excluded from the study. All women were treated with radical abdominal hysterectomy Piver type III [14] with systematic pelvic lymphadenectomy, but without para-aortic lymph node dissection. All patients with parametrial involvement and/or pelvic lymph node disease received adjuvant combined radiation therapy.

The pathological examination of the radical hysterectomy specimen was made in a standardized manner [15,16].

The pelvic lymph nodes were processed completely up to the size of 0.5 cm. Larger nodes were bivalved longitudinally and processed completely as well. From all blocks containing lymph nodes, three step sections were performed for routine histologic workup. The occurrence of any extranodal extension of the metastatic deposits outside the lymph node capsule, regardless of its extension, was recognized as extracapsular spread (ECS). The size of the extension of ECS into the perinodal fatty tissue was not determined.

All tumors were staged and classified according to the most recent WHO and TNM classifications [17,18].

Follow-up data regarding recurrent disease and death were obtained from the clinical files. There was a written informed consent was obtained form the patient for the use of the data.

Overall survival and recurrence-free survival were analysed using Kaplan–Meier curves and log-rank test. Five years overall and recurrence-free survival rates with 95% confidence intervals (CI) are given. Categorical data were analyzed by χ^2-test. Mann–Whitney U test were used for comparisons of continuous data. p-values less than 0.05 were considered as statistically significant. To assess the independent impact of extracapsular spread on overall survival a cox regression model was fitted. Lymphvascular space involvement, tumor grade, laterality of pelvic lymph node involvement, size of metastatic deposits in the pelvic lymph nodes, number of involved nodes and tumor stage were included in the model to adjust for. Relative risks (RR) with 95% confidence intervals (95% CI) are given. All statistical analyses were performed using the software package SPSS for Windows®, release 11.5.1 (SPSS GmbH Munich, Germany).

Results

Two hundred fifty-six patients were obtained from our files fulfilling the above mentioned criteria. Their characteristics are given in Table 1. The median follow-up time was 62 months (95% confidence interval 51 to 73 months).

Seventy-nine of the patients (30.9%) with pelvic lymph node involvement showed extracapsular extension of the metastatic deposits (ECS; Fig. 1).

Stage pT2 tumors showed a significant increase of ECS when compared with tumors confined to the cervix uteri (35.2% in stage pT2 versus 21.8% in pT1b; $p=0.024$). There was a significant association between the size of pelvic lymph node metastases and the occurrence of ECS (Fig. 2). The median size of metastatic deposits without ECS was 5 mm (min=1; max=32) compared to 12 mm (min=2; max=50) in cases with ECS ($p<0.001$). Additionally, there was a significant difference in the number of involved nodes for patients with and without ECS (Fig. 3).

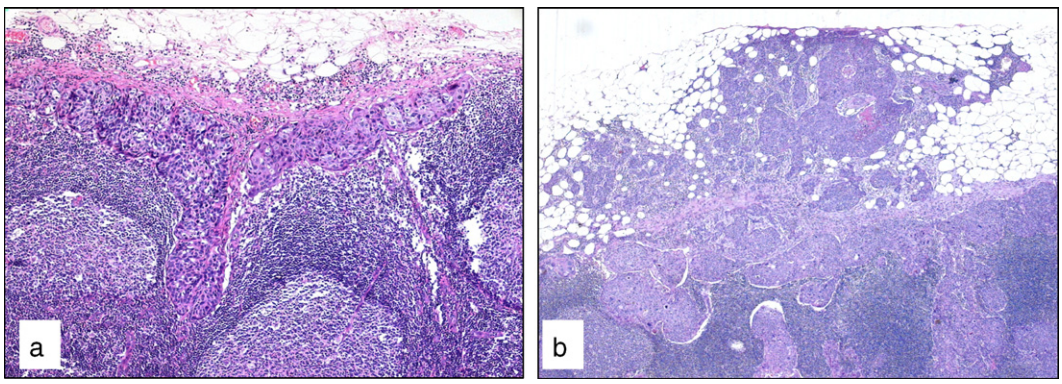

Fig. 1. Pelvic lymph node metastasis: Subcapsular localization of metastasis of squamous cell carcinoma of the cervix uteri without (a) and with (b) extracapsular spread (H&E staining, 214× and 109×).

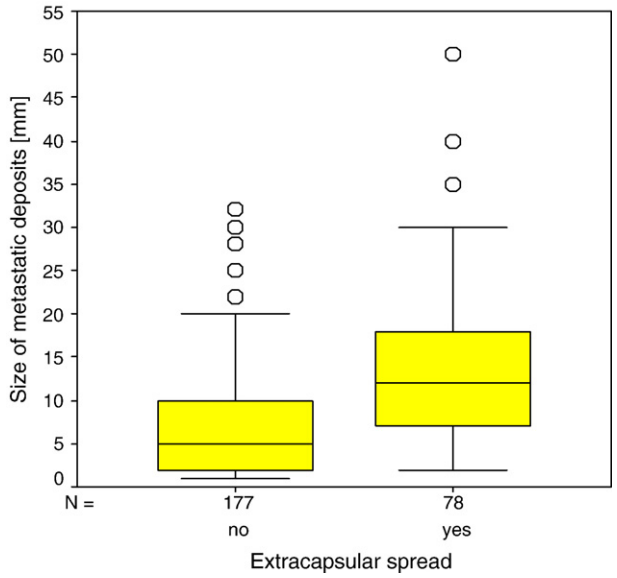

Fig. 2. Correlation of the size of the metastatic deposits and the occurrence of extracapsular spread.

Follow-up information was available for 247 out of the 256 cases (96.5%). These patients with complete follow-up information were used for the analysis regarding recurrent disease and survival analyses.

Patients with ECS showed a significant higher risk of recurrent disease and a reduced overall survival (Fig. 4). The 5-year recurrence-free survival rate in patients with ECS was 59.7% [95% CI: 46.3%–73.2%] compared to 67.2% [95% CI: 58.9%–75.5%] in patients without ECS ($p=0.04$).

The 5-year overall survival rate in patients with ECS was 33.5% [95% CI: 20.6%–46.3%] compared to 60.5% [95% CI: 52.3%–68.6%] in patients without ECS ($p<0.001$).

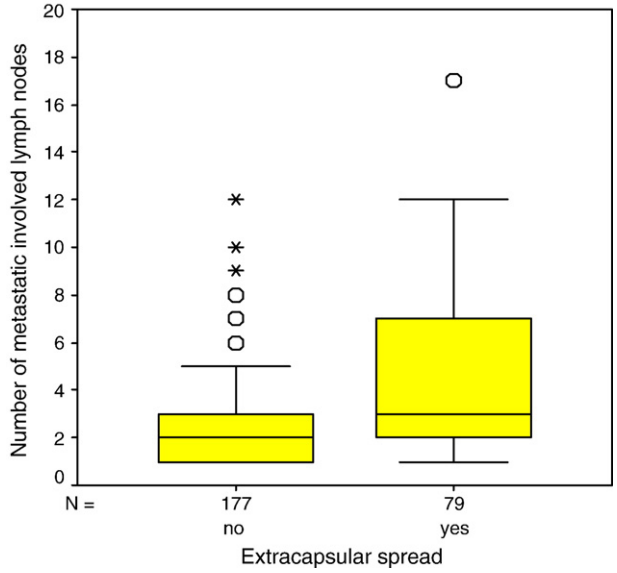

Fig. 3. Correlation of metastatic involved nodes and the occurrence of extracapsular spread of the metastatic deposits. The values of two patients with 33 and 50 involved nodes and extracapsular extension of the metastatic deposits are not shown.

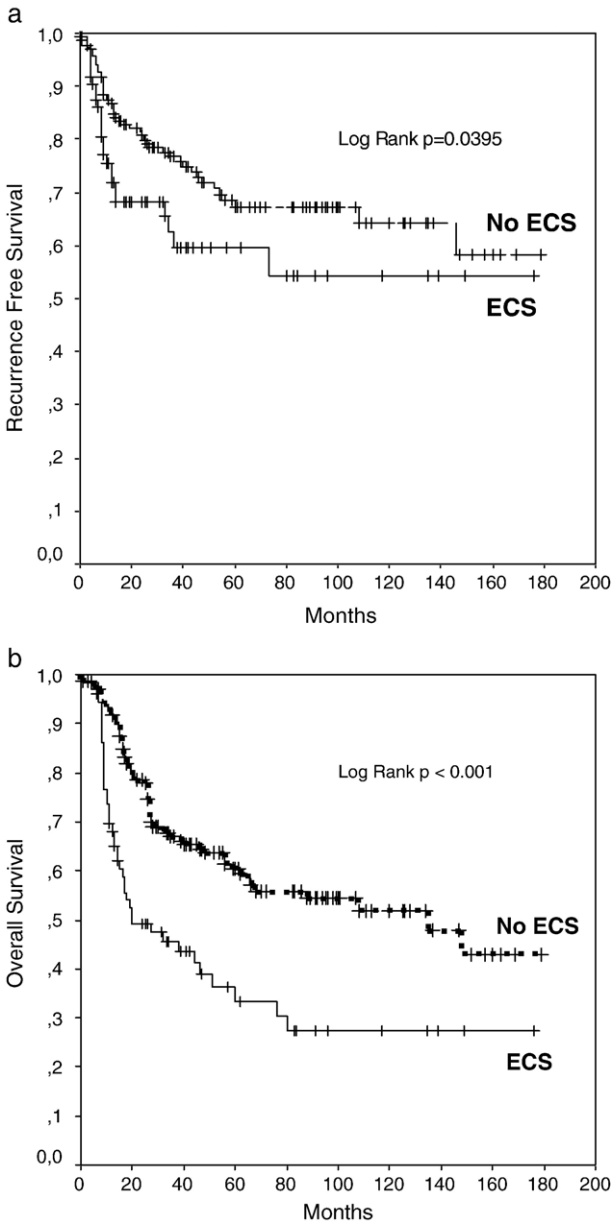

Fig. 4. Recurrence-free survival (a) and Overall survival (b) in patients with (lower curve) and without (upper curve) extracapsular spread of metastatic deposits in pelvic lymph nodes.

To assess the independent impact of ECS on overall survival, multivariate Cox regression model adjusted for lymphvascular space involvement, tumor differentiation (grading), laterality of pelvic lymph node involvement, size of metastatic deposits in pelvic nodes, number of involved nodes and tumor stage was performed. The results are presented in Table 2.

Discussion

For nodal-positive oral tongue and vulvar cancer, the frequency of ECS has been reported to be 37.5% and 46%, respectively [19,20]. In carcinoma of the cervix uteri, ECS was seen in 41.8% and 47.3% [4,10]. In the present study, the frequency of ECS was 30.9%. The differences in the frequency of

Table 2
Multivariate analysis of prognostic factors regarding overall survival in patients with carcinoma of the cervix uteri and pelvic lymph node involvement

		RR 95% CI	*p*-value
Extracapsular spread in nodal-positive cases			
No	Reference		
Yes	1.8	1.2–2.9	0.008
Number of involved pelvic nodes			
<3	Reference		
>3	1.8	1.1–3.0	0.027
Tumor grade			
G1	Reference		
G2	1.0	0.6–1.7	0.923
G3	1.7	1.02–2.8	0.042
Tumor stage			
pT1b	Reference		
pT2	1.6	1.1–2.5	0.024
Size of metastatic deposits in pelvic lymph nodes			
<5 mm	Reference		
>5 mm	1.0	0.6–1.6	0.945
Laterality of pelvic lymph node involvement			
Unilateral	Reference		
Bilateral	1.0	0.6–1.5	0.866
Lymphovascular space involvement			
No	Reference		
Yes	0.9	0.5–1.6	0.761

ECS in these studies might be caused in the different numbers of cases included and the fact that the study of Morice et al. [4] examined patients with pelvic and para-aortal lymph node involvement as well. In vulvar cancer, the higher frequency of ECS might be caused by the different tumor biology of this tumor when compared to cervical carcinoma.

The prognostic impact of ECS has been intensively studied in cases of head and neck as well as oral cancer [5,6]. In this tumors as well as in breast cancer patients, ECS was associated with a higher rate of local failure and reduced 5-year survival [7,8]. Additionally, studies on vulvar cancer have identified ECS as an independent prognostic factor for reduced recurrence-free survival [9,20].

In the present study of 256 nodal-positive surgically treated CX, staged pT1b1 to pT2b, we showed that the occurrence of ECS was associated with an increased frequency of recurrent disease (33.8 vs. 27.7%; $p=0.295$) and a significant reduced 5-year overall survival rate (33.5% vs. 60.5%; $p<0.001$).

In an earlier study, Hale et al. [11] examined 49 cases of surgically treated FIGO-stage IB/IIA CX and failed to demonstrate any prognostic impact of ECS regarding treatment failure and tumor related death, respectively. Samlal et al. [10] have reported a reduced 5-year disease specific survival in their study of 134 node-positive patients (FIGO-stage IB and IIA) representing ECS (56% vs. 78%). However, they failed to demonstrate any significance. Tinga et al. [12] reported a reduced overall survival in patients who represented either multiple positive pelvic nodes or one positive node with ECS.

To the best of our knowledge, the only larger study dealing with the parameter of ECS in CX is the report of Morice et al. [4], which represented a significant prognostic impact of ECS. These authors reported an overall 3-year survival rate of 75% for patients without and of 40% for those representing ECS ($p<0.0001$). There was a 14.4 relative risk of tumor associated death for patients affected by ECS.

The cause for the higher frequency of local failure in patients with ECS is speculative at time. Perhaps, there is a higher risk of incomplete resection of tumor burden tissue at the site of nodal disease, presenting ECS. Because of the retrospective character of the present study, we were unable to determine the distance beween the extranodal tumor and the resection margin of the removed nodal tissue. To the best of our knowledge, there are no studies dealing with that issue in the literature.

Greenberg et al. [6] reported a significant correlation between the number of involved nodes and the occurrence of ECS in oral tongue cancer, as reported Palamba et al. [21] for breast cancer. In the present study, the occurrence of ECS showed a positive correlation to the number of involved pelvic nodes as well (see Fig. 3). So, it must be recommended that in patients with two or more involved lymph nodes, the positive nodes should be examined very carefully during pathologic workup to determine ECS.

For squamous cell carcinoma of the head and neck, Carter et al. [22] found that ECS was seen most frequently in association with large metastatic deposits. This is in concordance with our results. The median size of metastatic disease without ECS was 5 mm (min=1, max=32) compared to 12 mm (min=2; max=50) in cases with ECS ($p<0.001$; see Fig. 4).

In the present study, we have not determined the extent of ECS at the affected nodes (i.e. the maximum extension of the invasion of the metastatic deposit into the paranodal fatty tissue). However, it has been reported that in patients with oral tongue cancer, a correlation was seen between the extent of extranodal spread and patients survival [6]. So, further studies dealing with the extent of ECS, including CX, might be of interest.

It is interestingly to note, that in the before last edition of the TNM-classification of malignant tumors, extracapsular spread was recognized in the N-classification of breast cancer, termed pN1iv [23]. However, in the recent edition this parameter was omitted [18]. In breast carcinoma, ECS was shown to be a prognosticator in disease-free survival; however, it was not proven to be an independent prognostic indicator when the total number of positive nodes and the size of metastatic focus were added to the equation [8]. This is the probable reason why ECS was dropped from the 6th edition of the TNM staging manual for the staging of breast carcinoma.

However, in the present analysis of 256 surgically treated CX, staged pT1b to pT2b, we showed that patients with pelvic lymph node involvement and the occurrence of ECS represented a significant reduction of 5-year recurrence-free survival rate (59.7% vs. 67.2%; $p=0.04$) as well as a significant lower 5-year overall survival rate (33.5% vs. 60.5%; $p<0.001$). Furthermore, ECS represented as independent prognostic factor in multivariate analysis.

Abstracting the data from our study and those obtained from the literature, the presence of ECS should be determined by careful examination of the lymphadenectomy specimens of CX and the occurrence of ECS should be given in the pathologic oncology report. As mentioned above for breast cancer, we would recommend to include the fact of ECS in the classification

of nodal involvement in addition to the N-classification in the following manner:

- ECS 0 = lymph node involvement without extranodal spread of the metastatic deposits.
- ECS 1 = lymph node involvement with extranodal spread of the metastatic deposits.

This new category might be helpful in better prognostic discrimination of patients affected by metastatic lymph node disease in carcinoma of the cervix uteri.

Acknowledgments

The authors would like to thank Mrs. Karola Koschke for her help in collecting clinico-pathologic data for multivariate analysis.

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