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Detection of micrometastases in pelvic lymph nodes in patients with carcinoma of the cervix uteri using step sectioning: Frequency, topographic distribution and prognostic impact

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Abstract

Objectives. Limited information exist about the frequency of micrometastases, their topographic distribution and prognostic impact in patients with cervical carcinoma (CX).

Methods. Lymph nodes of patients with surgically treated CX, FIGO IB to IIB, with pelvic lymph node involvement, were re-examined regarding the size of metastatic deposits, their topographic distribution within the pelvis. Lymph node status (pN0 vs. pN1mic = metastasis < 0.2 cm vs. pN1 = metastasis > 0.2 cm) was correlated to recurrence free (RFS) and overall survival (OS).

Results. 31.4% of all patients (281/894) represented pelvic lymph node involvement. 22.2.% of the node positive ones showed micrometastases (pN1mic). Most commonly, obturator and internal nodes were affected by pN1mic, without any side differences. Patients with macrometastases (pN1) and micrometastases (pN1mic) represented significant reduced RFS-rate at 5-years (62% [95% CI: 54.2 to 69.8] for pN1 and 68.9% [95% CI: 55.5 to 82.4] for pN1mic) when compared to patients without metastatic disease (91.4% [95% CI: 89.0 to 93.8]; $p<0.001$) The 5-years OS-rate was decreased in patients with metastatic disease (pN0: 86.6% [95% CI: 83.7 to 89.5], pN1mic: 63.8% [95% CI: 50.9 to 76.7], pN1: 48.2% [95% CI: 40.4 to 56.0]; $p<0.0001$). These differences persisted in detailed analysis within these subgroups. In multivariate analysis, tumor stage, pelvic lymph node involvement and micrometastases were independent prognostic factors.

Conclusions. A remarkable number of patients with CX show micrometastases within pelvic nodes. Micrometastatic disease represents an independent prognostic factor. So, all patients with pelvic lymph node involvement, including micrometastatic deposits, might be candidates for adjuvant treatment.

Keywords: Cervical carcinoma; Pelvic lymph nodes; Metastases; Metastatic disease; Micrometastases; Occult tumor cells; Prognosis; Sentinel lymph node

Introduction

Apart from tumor stage, studies indicate that lymph node metastases are an independent prognostic factor for recurrence free and overall survival [1–3].

The number of involved nodes, the size of macrometastatic deposits, the site and number of nodal sites involved and the occurrence of extracapsular extension of the metastases are also mentioned as prognosticators [2,4,5]. In breast, gastric and colorectal cancer, micro-metastatic disease (MM) has been reported as prognostic indicator [6–8].

Under consideration of the sentinel lymph node technique in CX, few articles dealing with the detection of MM in pelvic lymph nodes [9–12]. However, the exact frequency of MM, their topographic distribution and their prognostic impact is still not well determined. In order to address these issues, we examined surgically treated CX regarding the occurrence of MM and their prognostic impact.

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Material and methods

Data from patients with CX, staged FIGO IB to IIB were obtained from the files of our Wertheim-Archive [13]. Patients who received neoadjuvant therapy, those with incomplete local tumor resection (R1-resection = microscopic tumor at the resection margins of the radical hysterectomy specimen or R2-resection = macroscopic tumor at the margins) and tumors of other histologic type as squamous cell and adenocarcinomas were excluded from the study. All women were treated with radical abdominal hysterectomy Piver type III [14]. All patients with parametrial involvement received adjuvant combined radiation therapy without concurrent chemotherapy. The same treatment was administered to all patients affected by pelvic lymph node involvement, regardless of the size of the metastatic deposits.

The pathological examination of the radical hysterectomy specimen was made in a standardised manner [15,16]. All tumors were staged and classified according to WHO- and TNM-classification [17,18].

The resected lymph nodes were handled in a standardised manner [19] and were processed completely up to the size of 0.5 cm. Larger nodes were bivalved longitudinally and processed completely as well, routinely performing three step sections. All metastatic deposits were detailed measured using an ocular micrometer. There was no recutting of the archival material and the measurement was performed on the original slides. No anciliar techniques were used for identifying metastatic disease. According to previous publications and the recommendations of the American Joint Committee for Cancer Staging (AJCC) for breast cancer [20–22], the term micrometastasis (MM) was defined as a metastatic deposit within the lymph nodes constituting < 0.2 cm in largest dimension. As recommended in the TNM-classification for breast cancer [18], the detection of MM was termed as pN1mic. Metastatic deposits larger than 0.2 cm were defined as macrometastases and termed pN1. Those patients who showed solely metastatic deposits < 0.2 cm within largest dimension in the affected nodes were defined to have micrometastatic disease. Contrary, all patients who represented metastatic deposits lower and larger 0.2 cm or those who showed solely lymph node involvement > 0.2 cm were stated to have macrometastatic disease.

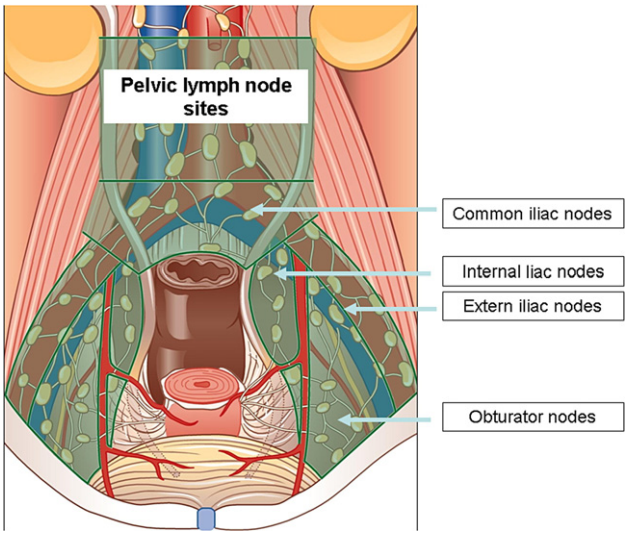

Fig. 1. Topographic sites of pelvic nodes (see text).

Table 1
Patients characteristics

Median age: 41 years (range 20–74 years)		
Stage distribution		
pT1b1	480	(53.7%)
pT1b2	91	(10.2%)
pT2a	75	(8.4%)
pT2b	208	(23.3%)
unknown	40	(4.5%)
Lymphovascular space involvement		
none	308	(34.4%)
yes	586	(65.6%)
Pelvic lymph node involvement		
none	613	(68.6%)
yes	281	(31.4%)
Size of the metastatic deposits within pelvic nodes (see text)		
micrometastases	59	(22.2%)
macrometastases	207	(77.8%)
Tumor grade		
G1	349	(39.1%)
G2	309	(34.6%)
G3	236	(26.3%)
Recurrent disease [a]		
none	757	(82.2%)
yes	135	(17.8%)

[a] For 2 cases no information regarding status of recurrent disease was available.

The lymph nodes of all patients who were reported as node negative in the initial oncologic pathology report, were not re-examined for pelvic lymph node involvement in the present study.

Since no national or international guidelines are available for classifying the topography of lymph nodes, we cartographed the localization of lymph nodes according to previous studies [23–25] and our surgical procedure as given in Fig. 1.

Follow-up data were obtained from the clinical files. There was a written informed consent obtained form the patient for the use of the data. Additionally, the study was approved by the Institutional Review Board.

Survival data were analysed using Kaplan–Meier-curves and log-rank-test. 5-years overall and recurrence free survival rates with 95% confidence intervals (CI) are given. Categorical data were analyzed by Chi^2-test and continuous data by Mann–Whitney *U* test. *P*-values less than 0.05 were considered as statistically significant. To assess the independent impact of micrometastatic disease on overall survival a cox regression model was fitted, using the software package SPSS for Windows®, release 15.5.1 (SPSS GmbH Munich, Germany).

Results

The median follow up-time was 82 months [95% CI: 72 to 95 months].

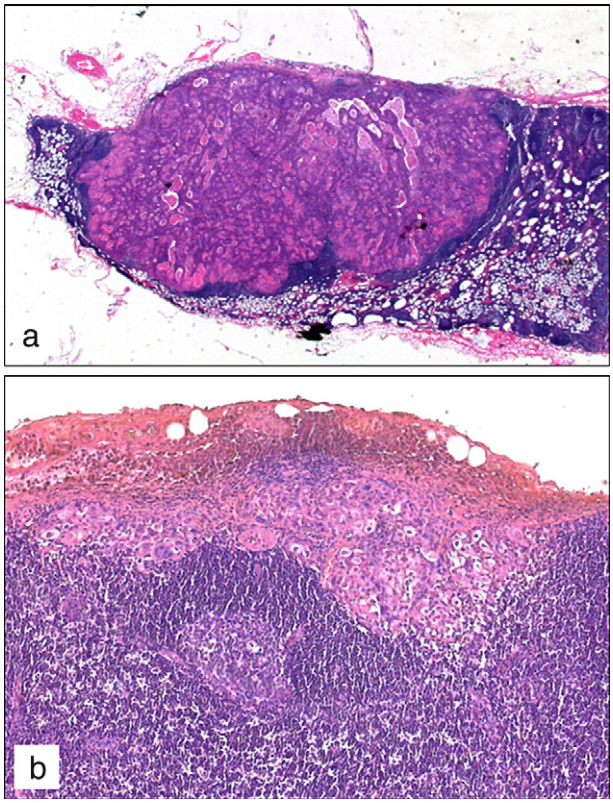

Fig. 2. Histologic pictures from metastatic deposits of a squamous cell carcinoma of the cervix uteri in pelvic lymph nodes, representing macrometastatic (a: H&E-staining, 75×) and micrometastatic disease (b: H&E-staining, 215×; see text).

The median number of resected pelvic nodes was 29 (range 2 to 72 nodes). The majority of patients (93.9%) received radical pelvic lymph node resection (>20 pelvic nodes). In 55 patients, representing 6.1% of all patients, lower than 20 pelvic nodes were removed (Table 1).

31.4% (281/894) of all patients represented with pelvic lymph node involvement. In 15 patients the size of the metastatic deposits was not available, because the edges of the metastatic deposits were cut during macroscopic preparation and processing of the material. 22.2% of the remaining, node positive, patients (59/266) showed micrometastases (pN1mic; Fig. 2) and 77.8% macrometastatic disease (pN1).

The majority of cases in the micrometastatis group had only one single identified metastatic deposit. But, 11 patients (11/59=18.9%) showed more than one metastatic lymph node involvement, albeit each metastatic deposit being<0.2 cm in maximum size.

The topographic distribution of the micro- and macrometastatic sites is given in Fig. 3. There was no significant difference between the distribution of the lymph node metastases depending from their size (micro- versus macrometastases; $p>0.05$).

About 65.6% of all patients showed lymphovascular space involvement (LVSI), representing strong correlation between LVSI and pelvic lymph node involvement ($p<0.01$), but there was no correlation between LVSI and the detection of micro- and macrometastases ($p=0.45$; data not shown).

In comparison with node negative patients the relative risk to die adjusted for grading and stage for patients with micrometastases increased to 2.5 [95% CI: 1.5–4.0, $p=0.0002$] and for patients with macrometastases to 3.4 [95% CI: 2.4–4.7, $p<0.0001$]. Furthermore, patients with macrometastases showed an estimated relative risk for overall survival of 1.4 [95% CI: 0.9–2.2] when compared to patients affected by micrometastatic disease.

Patients with macrometastases (pN1) and those with micrometastatic disease pN1mic) represented significant reduced recurrence free survival (5-year RFS of 62% [95% CI: 54.2 to

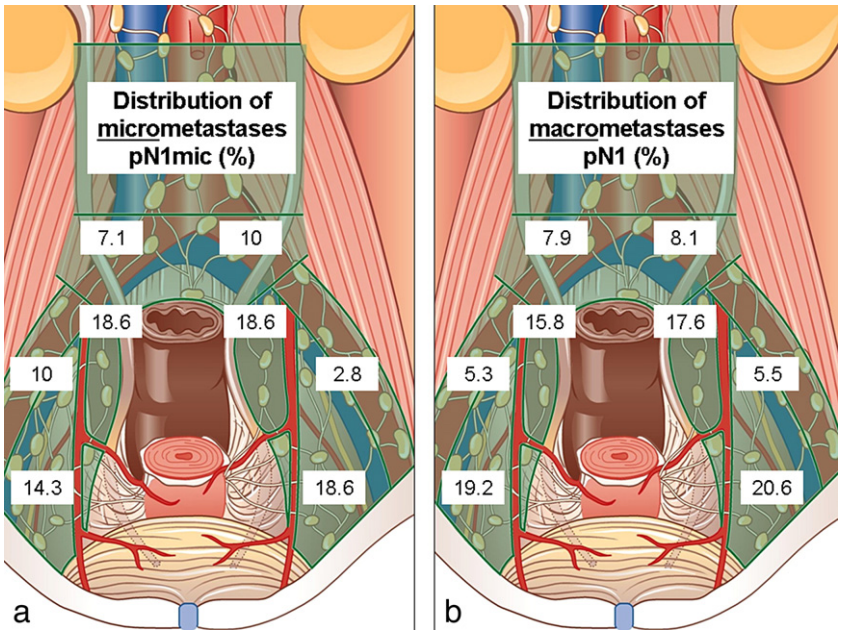

Fig. 3. Topographic distribution of the micro- and macrometastases.

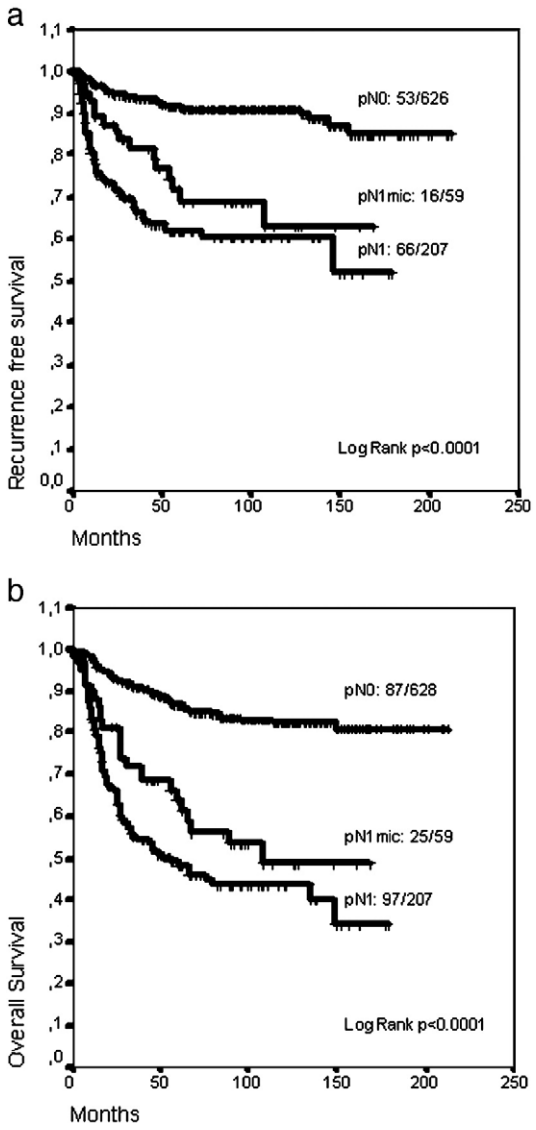

Fig. 4. (a) Kaplan–Meier-curve for recurrence free survival in patients. without pelvic lymph node involvement (pN0) and patients with micrometastatic (pN1mic) and macrometastatic disease (pN1) within the nodes (b) Kaplan–Meier-curve for overall survival in patients without pelvic lymph node involvement (pN0) and patients with micrometastatic (pN1mic) and macrometastatic disease (pN1) within the nodes.

69.9] for pN1 and of 68.9% [95% CI: 55.5 to 82.4] for pN1mic) when compared to node negative cases (5-year RFS-rate of 91.4% [95% CI: 89 to 93.8]; $p<0.001$; Fig. 4a). Also, the 5-year-overall-survival-rate was significantly decreased in patients with metastatic disease (pN0: 86.6% [95% CI: 83.7 to 89.5]; pN1mic: 63.8% [95% CI: 50.9 to 76.7]; pN1: 48.2% [95% CI: 40.4 to 56]; $p<0.001$; Fig. 4b). In that setting, the statistical significance for overall survival persisted in detailed analysis of the subgroups. Patients with micrometastases represented a 2.5 [95% CI: 1.5–4.0] and those with macrometastases a 3.4 [95% CI: 2.4–4.7] higher risk to die of the disease when compared to node negative patients ($p<0.001$). Furthermore, patients with macrometastases showed a relative risk of 1.6 [95% CI: 0.9–2.1] to die of the disease when compared to patients affected by micrometastatic disease. But, this difference showed only borderline significance ($p=0.058$).

The present study includes patients with a wide range of stage distribution (see Table 1) and all patients were primarily treated by surgery. But, nowadays patients with local advanced disease (FIGO stage IB2 and IIB) might be candidates to be treated with chemotherapy and radiation. To analyse the impact of micrometastases in early stage and local advanced disease, patients with stage pT1b1 and pT2a were grouped together and compared with patients affected by pT1b2 and pT2b stage disease. In that analysis there was also a difference within overall as well as for recurrent free survival (Table 2). But, there was no difference when cases with micro- and macrometastatic disease were compared regarding the impact on recurrence free and overall survival (data not shown).

To assess the independent impact of micrometastatic disease on overall survival, multivariate Cox regression was performed (see Table 3).

Discussion

The comprehensive pelvic lymphadenectomy should obtain at least 20 lymph nodes to insure the real condition of pelvic tumoral spread [10,26,27,28]. In the present study, a median number of 29 pelvic nodes (range 2–72) were removed. The frequency of incomplete pelvic lymphodectomy was 6.1% in our study which meets the data of previous paper [12,29,30].

The frequency of micrometastases (MM) in gynaecologic and non-gynecologic malignancies ranges from 8%–20.7% [7,8,31]. In surgical treated cervical cancer patients with and without the use of sentinel lymph node (SLN) technique, a mean frequency of 12.9% (3.8–23.9%) for MM has been reported [9,10,12,29,32]. The higher frequency *n* the present study

Table 2
Prognostic impact of pelvic lymph node micro- and macrometastases within different stages of the disease (see text)

	pN0	pN1mic	pN1
All cases (pT1b1 to pT2b)			
5-years recurrent free survival	91.4% [95% CI: 89 to 93.8]	68.9% [95% CI: 55.5 to 82.4]	62.0% [95% CI: 54.2 to 69.9] *
5-years overall survival	86.6% [95% CI: 83.7 to 89.5]	63.8% [95% CI: 50.9 to 76.7]	48.2% [95% CI: 40.4 to 56] *
pT1b1 and pT2a			
5-years recurrent free survival	93.5% [95% CI: 91.0 to 96.0]	86.7% [95% CI: 69.5 to 100]	73.1% [95% CI: 61.3 to 84.9] *
5-years overall survival	89.9% [95% CI: 87.0 to 92.8]	75.6% [95% CI: 57.0 to 94.2]	56.5% [95% CI: 43.8 to 69.2] *
pT1b2 and pT2b			
5-years recurrent free survival	84.4% [95% CI: 77.9 to 90.9]	57.1% [95% CI: 38.7 to 75.5]	57.3% [95% CI: 46.5 to 68.1] *
5-years overall survival	76.3% [95% CI: 68.7 to 83.9]	55.6% [95% CI: 38.4 to 72.8]	46.6% [95% CI: 36.2 to 57.0] *

* $p<0.0001$.

Table 3
Multivariate analysis of prognostic factors regarding overall survival

	RR	95%-CI	*p*-value
Pelvic lymph node involvement			
None (pN0)	Reference		
Micrometastases (pN1mic)	2.5	1.5–4.0	0.0002
Macrometastases (pN1)	3.4	2.4–4.7	<0.0001
Tumor grade			
G1	Reference		
G2	1.1	0.8–1.6	0.6399
G3	1.6	1.1–2.3	0.0095
Tumor stage			
pT1b1	Reference		
pT1b2	1.5	0.9–2.5	0.1243
pT2a	2.2	1.3–3.6	0.0019
pT2b	2.5	1.7–3.7	<0.0001

(22.2%) might be caused by performing three step sections for routine workup of the nodes, confirming the evidence that step sectioning nodes increases the detection of metastatic disease in a variety of malignancies [32–34].

As shown in Fig. 3, the most frequent site of pelvic lymph node involvement were the obturator and internal nodes, without any differences within the right and the left hand side and without differences within the topographic distribution of micro- and macrometastases. Our data are in consistency within the results of recent studies dealing with the mapping of sentinel lymph nodes in cervical cancer [24,25,35,36]. In abstracting these results, our study indirectly supports the concept of sentinel lymph node technique in CX. Also in patients with local advanced cervical cancer and macrometastatic lymph node involvement, the obturator nodes are the most likely to be involved, followed by the internal and external iliac lymph nodes [37].

Sentinel lymph node studies in CX reported a rate of MM of 16.7% using immunohistochemistry [33,36,38,39]. But, in an earlier study we were unable to detect any additional lymph node involvement using immunohistochemical ultrastaging after performing step sectioning in routine histopathologic workup of all resected nodes in small FIGO stage IB1 nodal negative patients who were suffered by recurrent disease [34]. Similar results were reported by Cote et al. [33] for breast cancer. Based on these data, all lymph nodes (including sentinel nodes) in patients affected by CX should be examined by performing step sectioning and H&E-staining without performing anciliar techniques.

One disadvantage of the present study might be that all patients were treated before the introduction of chemotherapy or chemoradiation in the treatment approaches of CX. Consecutively, also patients with preoperative FIGO stage IB2 and IIB were surgically treated within the study period who are nowadays candidates for chemoradiation as primary treatment approach. But, in separate analysis of patients with stage pT1b1 and pT2a who are primarily treated by surgery in the most centers, micrometastases showed significant prognostic impact (see Table 2).

The management for cervical cancer with intraoperative positive pelvic lymph nodes, determined on frozen section is controversial. Sometimes radical hysterectomy is abandoned in that setting [41,42]. We found a borderline statistic significance regarding overall survival in a subgroup analysis comparing patients with micrometastases (pN1mic) with those having macrometastatic deposits (pN1) of $p=0.058$. So, also the intraoperative detection of micrometastases lymph node by frozen section, might be an indication to abandon the operation procedure, but because of the borderline significance in our study and the limited number of patients studied as well as the controversial results reported in the literature [41,42] further studies are strongly required dealing with that topic.

As reported earlier, the risk of recurrent disease in patients with MM was significant higher than for node negative patients [9,12,40]. We showed a significant higher risk of recurrent disease and a reduction of overall survival in patients with MM. Furthermore, micrometastases in pelvic lymph nodes represented an independent prognostic factor in multivariate analysis. So, all patients with pelvic lymph node involvement, regardless of the metastatic deposits represent micro- or macrometastases might be candidates for adjuvant treatment according to recent protocols.

Conflict of interest statement
The authors have no conflicts of interest to declare.

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