Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 111 (2008) 276–281
Gynecologic Oncology
www.elsevier.com/locate/ygyno

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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Received 16 May 2008
Available online 21 August 2008

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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doi:10.1016/j.ygyno.2008.07.017

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.

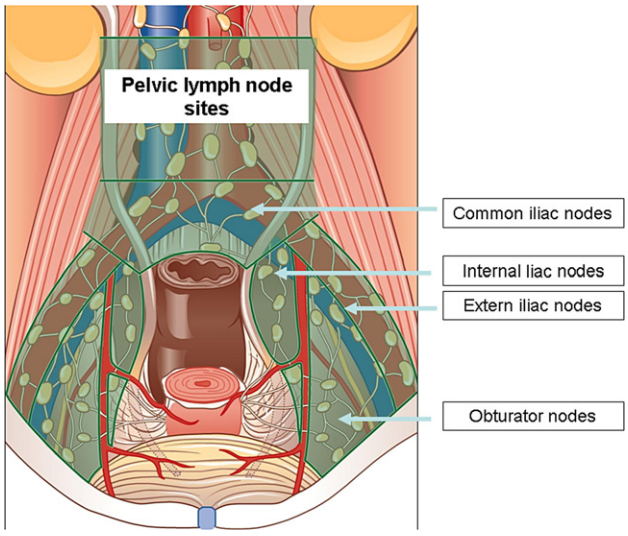

Fig. 1. Topographic sites of pelvic nodes (see text).

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].