Evaluation of prognostic significance in extracapsular spread of pelvic lymph node metastasis in patients with cervical cancer

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Summary

Background: Extracapsular spread of lymph node (LN) metastasis has been shown as a negative prognostic factor in cancers of several organs. This study was performed to clarify the prognostic significance of extracapsular spread of pelvic lymph node metastases in patients who underwent radical hysterectomy and pelvic, paraaortic lymphadenectomy for International Federation of Gynecology and Obstetrics (FIGO) Stage I-II cervical carcinoma. *Methods:* Ninety-five patients were treated wih radical hysterectomy and pelvic paraaortic lymphadenectomy for Stage I-II cervical carcinoma. Twenty-one cases with positive nodes of the tumor and lymph nodes were reviewed. The describtion of the pattern of metastasis present in the node was focused on: maximal diameter of metastasis was compared with the maximal diameter of the node, the capsular integrity, and the type of immune response. The prognostic significance of extracapsular spread (ECS), maximal diameter of metastasis and the type of immune response of pelvic metastases was evaluated with respect to disease-free survival (DFS), overall survival, and the pattern of disease recurrence. *Results:* ECS was seen in 52.4% (11/21) of the cases. The 5-year DFS rate in patients with ECS was significantly lower compared to patients without ECS (63.4% vs 100%; p = 0.03). To assess the independent impact of ECS on overall survival, the multivariate Cox regression model was not significantly different. *Conclusion:* From data in our study and those obtained from the literature, the occurence of ECS should be given in the pathology report. Including ECS in the classification of nodal involvement might be helpful in better prognostic discrimination of patients with metastatic lymph nodes.

Key words: Cervix carcinoma; Pelvic metastasis; Extracapsular spread.

Introduction

Patients with FIGO Stage I and IIa are preferentially treated with radical hysterectomy and pelvic lymph node dissection, achieving 5-year survival rates of approximately 88% [1, 2]. In spite of early disease state, a number of patients will recur, and most of these will eventually die of the disease. Therefore, determination of prognostic factors is required for discrimination between high and low-risk groups among this group. Individual parameters that predict poor prognosis have been the subject of many publications [1-4]. Studies indicate that the presence of lymph node metastases (LNM) is an independent prognostic factor for overall and disease-free survival (DFS), and local recurrence in carcinoma of the uterine cervix [5]. We showed that 22.1% of patients with Stage I-II cervical cancer had positive pelvic nodes.

Studies have shown that different types of lymph node metastases have different prognostic significance in the head and neck, breast, and vulvar carcinoma [6-8]. Despite this, there are only a limited number of studies in the literature addressing the prognostic significance of the pathologic pattern of pelvic lymph node metastases in early-stage cervical carcinoma [9-13].

The aim of this study was to correlate the pathologic patterns of pelvic lymph node metastases according to survival and recurrence rates in early-stage cervical carcinoma.

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Material and Method

During the period from 1995 to 2000, 95 patients with early-stage cervical cancer were managed surgically at Ankara Oncology Research and Education Hospital.

We included patients with Stage I-II who were clinically staged as recommended by FIGO and excluded patients with paraaortic lymph node involvement. Histologic classification was performed according to the World Health Organization classification [14].

All patients underwent a staging laparotomy, radical hysterectomy, and bilateral pelvic and periaortic lymphadenectomy. All surviving patients were followed-up at least 60 months with a median follow-up of 100 months (range, 5-120 months). Pathological and clinical data and follow-up information were retrieved from the medical records. The selection of postoperative adjuvant therapy was at the discretion of the attending gynecologic oncologist in charge of the patient. Generally, patients with LNM, parametrial invasion, positive or close surgical margins, lymphovascular space invasion (LVSI) with deep stromal invasion were considered for adjuvant radiotherapy (RT) or chemoradiotherapy (CT+ RT). A total of 76 patients received external beam radiation consisting of pelvic radiotherapy followed by vaginal brachytherapy or chemoradiotherapy. The protocols of postoperative chemotherapy included cisplatin-based regimens for four to six courses. Pelvic radiation was given at daily 2 Gy for a total dose of 50 Gy. Remote afterloading of intravaginal iridium-192 brachytherapy was placed one to two weeks after completion of external RT, delivering in 21 Gy/7 fractions within two weeks.

A chart review was performed to determine clinical outcomes including time to recurrence, salvage therapies, and survival.

All 21 patients with positive nodes had slides of the tumor and lymph nodes reviewed. A maximum of four positive pelvic lymph nodes was reviewed in every patient. When there were more than four, the node with the maximal diameter was always reviewed plus another three randomly chosen nodes. Owing to the retrospective nature of the study, only two of the three dimensions of the lymph nodes were available for measurements on the histologic section. The description of the pattern of metastasis present in the node was focused on: the maximal diameter of metastasis compared with maximal diameter of the node, capsular integrity, and type of immune response.

Extracapsular metastasis was defined as the extention of tumor through the capsule of the lymph node into the perinodal tissue. A patient had extracapsular metastasis if the above histologic pattern was present at least in one lymph node. The patterns of immune response were defined as follows: 1) lymphocyte predominance, when there was an increased number of small lymphocytes throughout the cortex, paracortex, and medullary regions; 2) germinal center predominance, when germinal centers containing large lymphoid cells and mitotic figures extended throughout the cortex and paracortex; 3) Unstimulated, when there were lymphoid follicles without germinal centers in the cortex and hypocellular paracortical areas [15, 16]. When there was a mixed immune pattern within an individual node, the lymph node was designated according to that pattern occupying the greatest area within it. When there were different lymph nodes with different types of immune pattern within the same patient, we classified the case according to the worst pattern reported in the literature for other tumors [16].

For the analysis of the diameter of lymph node metastasis, a cutoff of 2 mm was chosen on the basis of the existing literature on other tumors [8], which defined as micrometastases those measuring < 2 mm.

Statistics

Statistical analysis was performed using the "SPSS 10.05 for Windows" computer program. The follow-up interval was calculated in months and defined as the time between the date of surgery and date of the event (death, distant or local recurrence) or last follow-up. When DFS is used as an endpoint, an event includes the first documented recurrence of disease. DFS rates were calculated by the Kaplan-Meier method, and the log rank test was used for comparison. The stepwise Cox proportional hazard model was used to assess the independent prognostic and predictive factors affecting DFS; *p* values of less than 0.05 derived from two-tailed tests were considered significant.

Results

Median age was 48 (19-74) years and five-year survival was 87.1%. Characteristics of patients are shown in Table 1.

Eleven patients (52.4%) with pelvic lymph node involvement showed ECS of the metastatic deposits. Twelve patients (57.1%) with pelvic lymph node metastasis showed greater than 2 mm diameter of metastasis, and eight (38.1%) patients had lymphocyte predominance of immune pattern. Twelve patients (61.9%) had other immunologic patterns (Table 2).

The 5-year DFS rate in patients with ECS was 63.64% compared to 100% in patients without ECS (p = 0.0392). The 5-year DFS was not significantly different for immunologic pattern and maximal diameter of metastatic lymph nodes (Table 2).

To assess the independent impact of ECS on overall survival, multivariate analysis with Cox's regression model was not significantly different (p = 0.985).

Table 1. — *Patient characteristics.*

Characteristics	All patients Number (%)	Pelvic lymph node positive patients Number (%)
Median age	48 (range 19-74) years	50 (range 33-64) years
FIGO		
Stage I	67 (70.5)	17 (80.9)
Stage II	28 (29.5)	4 (19.1)
Histologic subtype		
Squamous	79 (83.2)	17 (81)
Non-squamous	16 (16.8)	4 (19)
Tumor diameter		
< 2	19 (20)	3 (14.3)
2-4	60 (63.2)	11 (51.4)
> 4	16 (16.8)	7 (33.3)
Grade		
1	50 (52.6)	9 (42.9)
2-3	45(47.4)	12 (57.1)
Lymphovascular invasion		
No	72 (75.8)	10 (47.6)
Yes	23 (24.2)	11 (52.4)
Parametrial involvement		
No	81 (85.3)	18 (85.7)
Yes	14(14.7)	3 (14.3)
Pelvic nodes		
Negative	74 (77.9)	
Positive	21 (22.1)	
Surgical margins		
Negative	89 (93.7)	17 (81)
Positive	6 (6.3)	4 (19)
Other - 1/3 stromal invasion		
No	63 (66.3)	13 (61.9)
Yes	32 (33.7)	8 (38.1)

Discussion

The association between size or volume of lymph node metastases and prognosis has also been previosly demonstrated in vulvar [6] and prostate cancer [17]. The presense of a tumor growing outside the capsule of the lymph node has been demonstrated to be of prognostic significance in squamous carcinoma of the head and neck [7], in the breast [8], and vulvar cancer [6].

Table 2. — *Univariate analysis of lymph node characteristics for 5-year disease-free survival (DFS).*

	Number (%)	5-year DFS	p log rank
Extracapsular spread			
No	10 (47.6)	100	0.0392
Yes	11 (52.4)	63.64	
Maximal diameter of lymph node			
≤ 2	9 (42.9)	100	0.0629
> 2	12 (57.1)	60.67	
Immunologic pattern			
Lymphosit predominance	8 (38.1)	62.50	0.0880
Other	13 (61.9)	92.31	

For nodal positive carcinoma of the uterine cervix, the frequency of ECS has been reported to be 41.8%, 47.3% and 30.9%, respectively [9, 10, 13]. In our study, the frequency of ECS was 52.4%. The differences in the frequency of ECS in these studies might be caused by the different numbers of cases included.

In our limited series, we showed reduced 5-year DFS in node-positive patients representing ECS ($p = 0.03$). To assess the independent impact of ECS on overall survival, Cox's multivariate regression model was not significantly different. Five-year survival was not significantly different for immunologic pattern and maximal diameter of metastatic lymph nodes. However the relatively small number of patients seen in this study limits the power of our calculations. Thus, further studies dealing with the immunologic pattern and maximal diameter of metastatic lymph nodes might be of interest.

Samlel *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 had positive nodes with ECS.

Two larger studies dealing with the parameters of ECS in cervical carcinoma are the report of Morice *et al.* [9] and Horn *et al.* [13] which demonstrated a significant prognostic impact of ECS. Morice *et al.* [9] examined 138 patients with pelvic and paraaortic lymph node involvement. These authors reported an overall 3-year survival rate of 75% for patients without and of 40% for those with ECS ($p < 0.0001$). Horn *et al.* [13] examined 256 surgically treated cervical carcinoma patients with Stage pT1b, pT2b. They showed that patients with pelvic lymph node involvement and the occurence of ECS represented a significant reduction in 5-year recurrence free survival rate (59.7% vs 67.2%, $p = 0.04$) as well as a significantly lower 5-year overall survival rate (33.5% vs 60.5%, $p < 0.001$). In their study, ECS represented as independent prognostic factor in multivariate analysis.

From data in our study and those obtained from the literature, the occurence of ECS should be given in the pathology report. The fact of ECS in the classification of nodal involvement might be helpful in better prognostic discrimination of patients with metastatic lymph nodes.

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