

Number and distribution of pelvic lymph nodes and effect of surgical pathologic factors on pelvic lymph node status in patients with early-stage cervical carcinoma treated with radical hysterectomy and pelvic lymph node dissection

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Summary

Purpose of investigation: To report the number and distribution of pelvic lymph nodes and to identify surgical pathologic factors that best predict positive pelvic lymph nodes in patients with early-stage cervical carcinoma treated with radical hysterectomy and pelvic lymph node dissection (RHND).

Methods: Data from the files of 126 patients with cervical carcinoma treated by RHND at the Soroka Medical Center from 1962 through 2005 were analyzed.

Results: The status of pelvic lymph nodes was known in 114 patients. The exact number of lymph nodes removed from the pelvis of each patient was known in 111 patients. The mean number of lymph nodes removed from the pelvis per patient was 26.6 (median 23; range 1-62). Positive pelvic lymph nodes were found in 35 (30.7%) of the patients with a mean of 3.4 (median 2; range, 1-15) positive pelvic lymph nodes per patient. In a univariate analysis, positive lymph vascular space invasion and positive parametrial and/or paracervical involvement were significant predictors of positive pelvic lymph nodes, whereas penetration $\geq 50\%$ of the thickness of the cervical wall and grade 2+3 were of borderline significance. In a multivariate analysis, positive lymph vascular space invasion was the strongest and the only significant predictor of positive pelvic lymph nodes, whereas positive parametrial and/or paracervical involvement was of borderline significance.

Conclusions: In patients with early-stage cervical carcinoma treated with RHND, positive lymph vascular space invasion emerged to be the strongest and most significant predictor of positive pelvic lymph nodes.

Key words: Cervical carcinoma; Lymph nodes; Prognostic factors; Lymph vascular space invasion.

Introduction

Surgical pathologic factors such as positive pelvic lymph nodes, positive parametrial and/or paracervical involvement, positive vaginal margin involvement, positive lymph vascular space invasion, tumor size ≥ 4 cm, penetration $\geq 50\%$ of the thickness of the cervical wall, close vaginal margin, poor differentiation, adenosquamous histologic type, glassy cell histologic type and clear cell histologic type have been identified to compromise the outcome of patients with early-stage cervical carcinoma (FIGO clinical Stages IA₂, IB₁, IB₂, and IIA) treated with radical hysterectomy and pelvic lymph node dissection (RHND) [1, 2]. High-risk factors such as positive pelvic lymph nodes, positive parametrial and/or paracervical involvement and positive vaginal margin involvement are considerably stronger than other high-risk factors in predicting adverse outcome; thus, they are often designated "hard" high-risk factors while the others are called "soft" high-risk factors [3]. In the presence of at least one "hard" high-risk factor or at least two "soft" high-risk factors, the tumor is designated "high-risk

early-stage cervical carcinoma" and the administration of postoperative adjuvant pelvic radiotherapy should seriously be considered as a method of improving local control and presumably survival [4-6]. In a previous study published in this journal [3], we have demonstrated that pelvic lymph node status is the strongest factor affecting administration of postoperative adjuvant radiotherapy and the most significant predictor of survival in patients with early-stage cervical carcinoma treated with RHND. The aim of the present study was to report the number, distribution and status of pelvic lymph nodes and to identify surgical pathologic factors that best correlated with positive pelvic lymph nodes in patients with early-stage cervical carcinoma treated with RHND.

Patients and Methods

The clinical and pathological records of 126 patients with early-stage cervical carcinoma (FIGO clinical Stages IA₂, IB₁, IB₂, and IIA) treated by RHND at the Soroka Medical Center, Beer-Sheva, Israel between January 1962 and October 2005 were reviewed. The surgical technique performed of RHND was consistent with a Class III extended hysterectomy as described by Piver *et al.* [7]. The pelvic lymph node dissection consisted of removal of all lymphatic tissue around the

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common, external, and internal iliac vessels and anterior to the obturator nerve. After a thorough record review, all patients were retrospectively staged according to the revised International Federation of Gynecology and Obstetrics (FIGO) staging system for gynecologic cancer [8]. The following data concerning histopathologic findings were retrieved from the files of the patients: lymph vascular space invasion (negative or positive), parametrial and/or paracervical involvement (negative or positive), degree of penetration of cervical wall (< 50% or ≥ 50%), grade (1 or 2+3), lower uterine segment involvement (negative or positive), histologic type (squamous cell carcinoma or other histologic types including adenosquamous carcinoma, glassy cell carcinoma, adenocarcinoma and clear cell carcinoma), vaginal margin involvement (negative or positive), tumor size (< 4 cm or ≥ 4 cm), and status (negative or positive) and number of pelvic lymph nodes removed from the various pelvic anatomical sites (common iliac artery, external iliac artery, internal iliac artery and obturator fossa).

The mean number of pelvic lymph nodes removed per patient was calculated by dividing the total number of pelvic lymph nodes removed by the number of patients in whom the exact number of pelvic lymph nodes removed was known. The mean number of pelvic lymph nodes removed from each pelvic anatomical site was calculated by dividing the total number of pelvic lymph nodes removed from each pelvic anatomical site by the number of patients in whom the exact number of pelvic lymph nodes removed was known. The mean number of positive pelvic lymph nodes removed per patient was calculated by dividing the total number of positive pelvic lymph nodes removed by the number of patients in whom at least one positive pelvic lymph node was found. The mean number of positive pelvic lymph nodes removed from each pelvic anatomical site was calculated by dividing the total number of positive pelvic lymph nodes removed from each pelvic anatomical site by the number of patients in whom at least one positive pelvic lymph node was found. Differences between patient groups were tested by the chi-square test with Fisher exact test [9]. Multivariate analysis with use of backward and forward stepwise logistic regression analysis [10] was conducted to evaluate the joint effects of surgical pathologic variables on positivity of pelvic lymph nodes. Only p values < 0.05 were considered statistically significant.

Results

Information with respect to the status (negative or positive) of pelvic lymph nodes was available for 114 patients. However, information with respect to the exact number of lymph nodes removed from the pelvis of each patient was available for 111 (97.4%) patients. The total number of pelvic lymph nodes removed from these 111 patients was 2,948 nodes; thus, the mean number of pelvic lymph nodes removed per patient was 26.6 (median 23; range 1-62). At least one positive pelvic lymph node was found in the pelvis of 35 (30.7%) patients. The total number of positive pelvic lymph nodes removed from these 35 patients was 119 nodes; thus, the mean number of positive pelvic lymph nodes per patient in patients with at least one positive pelvic lymph node was 3.4 (median 2; range 1-15). The distribution of removed pelvic lymph nodes in relation to pelvic anatomical sites is displayed in Table 1.

Univariate analysis employing the chi-square test with Fisher's exact test demonstrated that positive lymph vas-

Table 1. — Distribution of removed pelvic lymph nodes in relation to pelvic anatomical sites.

Site	Number of nodes removed per patient (n = 111)			Number of positive nodes removed per patient (n = 35)		
	Mean	Median	Range	Mean	Median	Range
Whole pelvis	26.6	23	1-62	3.4	2	1-15
Obturator fossa	11	9	0-45	1.3	1	0-5
External iliac	8.8	8	0-27	0.8	0	0-5
Internal iliac	3.1	1	0-20	0.8	0	0-6
Common iliac	2.8	2	0-13	0.4	0	0-10
Right pelvis	14.5	12.5	0-40	1.6	1	0-15
Obturator fossa	6.1	5	0-21	0.6	0	0-3
External iliac	4.4	3	0-21	0.4	0	0-5
Internal iliac	1.8	0	0-18	0.3	0	0-6
Common iliac	2.2	2	0-13	0.4	0	0-10
Left pelvis	11.1	10	0-30	1.6	1	0-8
Obturator fossa	4.9	4	0-25	0.7	0	0-3
External iliac	4.4	4.5	0-13	0.4	0	0-4
Internal iliac	1.2	0	0-12	0.5	0	0-5
Common iliac	0.6	0	0-8	0.1	0	0-2

cular space invasion ($p < 0.0001$) and positive parametrial and/or paracervical involvement ($p = 0.002$) were significant predictors of positive pelvic lymph nodes, whereas penetration ≥ 50% of the thickness of the cervical wall ($p = 0.057$) and grade 2+3 ($p = 0.071$) were of borderline significance (Table 2). Univariate analysis failed to demonstrate that positive lower uterine segment involvement, histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell

Table 2. — Univariate analysis of surgical pathologic factors in relation to pelvic lymph node status in patients with early-stage cervical carcinoma treated with RHND.

Factor	No. of patients	Pelvic lymph node status		p value
		Negative (%)	Positive (%)	
Lymph vascular space invasion				
No	69	58 (84.1)	11 (15.9)	<0.0001
Yes	42	18 (42.9)	24 (57.1)	
Parametrial/paracervical involvement				
No	83	64 (77.1)	19 (22.9)	0.002
Yes	28	12 (42.9)	16 (57.1)	
Penetration of cervical wall				
< 50%	42	34 (81.0)	8 (19.0)	0.057
≥ 50%	72	45 (62.5)	27 (37.5)	
Grade				
1	22	19 (86.4)	3 (13.6)	0.071
2+3	92	60 (65.2)	32 (34.8)	
Lower uterine segment involvement				
No	79	58 (73.4)	21 (26.6)	0.113
Yes	32	18 (56.2)	14 (43.8)	
Histologic type				
SCC	88	62 (70.5)	26 (29.5)	0.466
AS, GC, AC and CC	24	15 (62.5)	9 (37.5)	
Stage				
IA2+IB1	71	50 (70.4)	21 (29.6)	0.680
IB2+IIA	42	28 (66.7)	14 (33.3)	
Vaginal margin involvement				
No	95	64 (67.4)	31 (32.6)	0.772
Yes	16	12 (75.0)	4 (25.0)	
Tumor size				
< 4 cm	81	57 (70.4)	24 (29.6)	0.823
≥ 4 cm	33	22 (66.7)	11 (33.3)	

Note: Information regarding the pelvic lymph node status (negative or positive) was available for 114 patients. Some factors were not available for all patients; therefore the number of patients in some of the patient groups adds up to less than 114. SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

Table 3. — Multivariate analysis (logistic regression) of surgical pathologic factors with endpoint positive pelvic lymph nodes in patients with early-stage cervical carcinoma treated with RHND.

Factor	Odds Ratio	95% confidence interval	p value
Lymph vascular space invasion			
No	1.000	Reference	
Yes	5.264	1.914-14.477	0.001
Parametrial/paracervical involvement			
No	1.000	Reference	
Yes	2.883	0.995-8.353	0.051
Grade			
1	1.000	Reference	
2+3	2.537	0.607-10.610	0.202
Penetration of cervical wall			
< 50%	1.000	Reference	
≥ 50%	0.826	0.262-2.604	0.745

carcinoma, Stage IB₂ + IIA, positive vaginal margin involvement and tumor size ≥ 4 cm were significant predictors of positive pelvic lymph nodes (Table 2). In a multivariate analysis with use of backward and forward stepwise logistic regression analysis, positive lymph vascular space invasion was the strongest and the only significant predictor of positive pelvic lymph nodes (p = 0.001), whereas positive parametrial and/or paracervical involvement was of borderline significance (p = 0.051) (Table 3). The risk of positive pelvic lymph nodes showed a 5.2-fold increase (95% confidence interval, 1.914-14.477) for positive over negative lymph vascular space invasion (Table 3).

Discussion

Systematic pelvic lymphadenectomy should aim to remove all lymphatic fatty tissue around and between the major pelvic blood vessels and in the obturator fossa. The number of removed pelvic lymph nodes reflects the thoroughness of the procedure. In 1967, the FIGO stated that a systematic lymphadenectomy should remove at least 20 nodes from the whole pelvis [11, 12]. In this study, the mean number of lymph nodes removed from the pelvis per patient was 26.6 (median 23; range 1-62); equal numbers of lymph nodes were removed from each side of the pelvis and the greatest number of removed nodes was obtained from the obturator fossa. This is in agreement with other studies that demonstrated that the mean number of lymph nodes removed from the pelvis per patient ranged from 26.1 to 46.6 and that equal numbers of lymph nodes were removed from each side of the pelvis [11, 13-16]. Girardi *et al.* [14] studied the historical development of pelvic lymph node dissection at their institution between 1971 and 1989. They noticed a significant increase in the mean number of pelvic lymph nodes removed per patient from 26.1 (median 24) for the first half of their study period to 37.4 (median 35) for the second half of their study period (p = 0.0001) [14]. In a series of 420 patients undergoing RHND for cervical carcinoma, Burghardt *et al.* [11] reported that the mean number of lymph nodes removed from the whole pelvis

per patient was 32.3 (median 32), the mean number of lymph nodes removed from the right side of the pelvis was 16.4 (median 16) and the mean number of lymph nodes removed from the left side of the pelvis was 15.2 (median 15). In a series of 875 patients undergoing RHND for cervical carcinoma, Inoue and Morita [15] observed that the mean number of pelvic lymph nodes removed per patient was 32 (range 9-73). Sevin *et al.* [16] demonstrated that the mean number of pelvic lymph nodes removed per patient in their series was 46.6.

Positive pelvic lymph nodes were found in 35 (30.7%) of the 114 patients reported in this study with a mean of 3.4 (median, 2; range 1-15) positive pelvic lymph nodes per patient. This is in agreement with other studies that demonstrated that 29.1%-55% of the patients with early-stage cervical carcinoma treated with RHND had positive pelvic lymph nodes with a mean of 3.6 positive pelvic lymph nodes per patient [11, 13-16]. Burghardt *et al.* [11] observed positive pelvic lymph nodes in 169 (40.2%) of their 420 patients with a mean of 3.6 (median 2) positive pelvic lymph nodes per patient. Girardi *et al.* [14] noticed a significant increase in the rate of positive pelvic lymph nodes over the years as follows: from 33% (63/195) in the years 1971-1979 to 55% (101/115) in the years 1981-1989 (p = 0.008). Inoue and Morita [15] reported the following positive pelvic lymph node rates: 29.1% overall (255/875), 22% for 484 Stage IB patients, 23% for 96 Stage IIA patients, and 43% for 295 Stage IIB patients. Of the 255 patients with positive pelvic lymph nodes, 98 (11.2%) had one positive node, 80 (9.1%) had two to three positive nodes, 45 (5.1%) had four to 18 positive nodes and 32 (3.7%) had unresectable positive nodes [15].

By means of univariate analysis, we have demonstrated that each of the following high-risk factors: positive lymph vascular space invasion and positive parametrial and/or paracervical involvement was a significant predictor of positive pelvic lymph nodes, whereas penetration ≥ 50% of the thickness of the cervical wall and grade 2+3 were of borderline significance. Univariate analysis failed to demonstrate that each of the following factors: positive lower uterine segment involvement, histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell carcinoma, Stage IB₂ + IIA, positive vaginal margin involvement and tumor size ≥ 4 cm was a significant predictor of positive pelvic lymph nodes. In a multivariate analysis, positive lymph vascular space invasion was the strongest and the only significant predictor of positive pelvic lymph nodes, whereas positive parametrial and/or paracervical involvement was of borderline significance. The risk of positive pelvic lymph nodes showed a 5.2-fold increase for positive lymph vascular space invasion over negative lymph vascular space invasion. These findings do not corroborate the study of Michel *et al.* [17] that demonstrated that clinical stage (p < 0.02) and tumor size (p < 0.001) are significant predictors of pelvic lymph node status.

In conclusion, in patients with early-stage cervical carcinoma treated with RHND, the mean number of

removed pelvic lymph nodes per patient was 26.6. Positive pelvic lymph nodes were encountered in 30.7% of the patients with a mean of 3.4 positive pelvic lymph nodes per patient. By means of univariate and multivariate analyses, we have demonstrated that positive lymph vascular space invasion is persistently the most significant predictor of positive pelvic lymph nodes.

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