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Surgical Pathologic Factors That Predict Recurrence in Stage IB and IIA Cervical Carcinoma Patients with Negative Pelvic Lymph Nodes

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BACKGROUND. The purpose of this analysis was to identify pathologic risk factors for recurrence and patterns of recurrence in patients with International Federation of Gynecology and Obstetrics Stage IB and IIA cervical carcinoma and negative pelvic lymph nodes after radical hysterectomy.

METHODS. During the period 1982–1991, 271 clinically staged patients with Stage IB or IIA cervical carcinoma underwent a Wertheim-Okabayashi radical hysterectomy with pelvic lymph node dissection. The study group was composed of 196 lymph node negative patients. Pathology slides were reviewed and multivariate analysis performed to identify independent prognostic factors.

RESULTS. The recurrence rate in the study group was 7.7%. In multivariate analysis, the following factors were identified as independent risk factors for recurrence: adenocarcinoma ($P = 0.003$), depth of invasion as a fraction of tumor penetration of the cervical stroma ($P = 0.01$), and an extensive stromal inflammatory cell infiltrate ($P = 0.04$). Based on these factors, the following risk groups were identified: a low risk group ($N = 140$, 5-year disease free interval [DFI] = 97%) and a high risk group ($N = 55$, 5-year DFI = 81%). An evaluation of the recurrence patterns for these patients showed a predominance of pelvic recurrences.

CONCLUSIONS. This study showed that among patients with Stage IB and IIA cervical carcinoma and negative pelvic lymph nodes, a subset with a significant risk for recurrence could be identified. Because the majority of recurrences in the lymph node negative group were pelvic recurrences, the value of adjuvant radiotherapy as a treatment for selected lymph node negative patients should be evaluated in a prospective study. *Cancer* 1997;80:1234–40.

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KEYWORDS: cancer of the cervix uteri, radical hysterectomy, negative lymph nodes, prognostic factors, recurrence.

Radical hysterectomy with pelvic lymphadenectomy is a widely accepted treatment for patients with Stage IB and IIA carcinoma of the uterine cervix.^{1–4} One of the most important critical determinants for prognosis is probably pelvic lymph node metastasis. The reported 5-year survival rate of patients with negative pelvic lymph nodes is approximately 90%, compared with 50–65% for patients with positive lymph nodes.^{1–6} It is therefore not surprising that efforts made to improve prognosis after radical surgery have mainly focused on the lymph node positive group.^{7–9} Unfortunately, a significant improvement in the survival of lymph node positive patients has not been achieved. Recently, several authors have pointed out that the lymph node negative group should be given more attention.^{1,10} Although the recurrence rate in this group is low, the absolute number of recur-

TABLE 1
Factors Significantly Related to Recurrence in Univariate Analysis

Factor	No. of patients	No. of recurrences (%)	P value
Tumor histology ^a			
Squamous cell carcinoma	158	9 (5.6)	0.04
Adenocarcinoma	37	6 (16.2)	
Tumor diameter			
<3 cm	120	5 (4.2)	0.02
≥3 cm	76	10 (13.1)	
Depth of invasion (mm)			
<10	119	5 (4.2)	0.01
≥10	77	10 (12.9)	
Depth of invasion as a fraction of cervical stroma penetration			
<2/3	110	3 (2.7)	0.007
≥2/3	86	12 (13.9)	

^a One patient with an undifferentiated carcinoma is not included.

rences in this group is at least equal to that in the lymph node positive group.^{1,11,12} Therefore, it seems worthwhile to put more effort into the identification of a subgroup of high risk lymph node negative patients and determine the sites of recurrence in these patients to establish whether they might benefit from adjuvant pelvic radiotherapy.

The aim of the current study was to determine whether surgical pathologic factors would predict recurrence in a group of Stages IB and IIA cervical carcinoma patients with negative pelvic lymph nodes. Furthermore, the recurrence pattern in this group was evaluated and compared with findings reported in the literature.

MATERIALS AND METHODS

The medical records of 271 patients with Stage IB and IIA cervical carcinoma who were treated with a Wertheim-Okabayashi radical hysterectomy and a complete pelvic lymphadenectomy were retrospectively reviewed. Staging was done according to guidelines of the International Federation of Gynecology and Obstetrics. Pathologic examination of the surgical specimens revealed negative pelvic lymph nodes in 218 patients and positive lymph nodes in 53 patients. Twenty-two lymph node negative patients in whom no residual tumor was found in the uterine specimen and whose biopsy slides were unavailable for review were excluded from the analysis. Disease did not recur in any of these patients. The remaining 196 lymph node negative patients constituted the study group. From these patients a variety of clinical and pathologic data, follow-up data, and recurrence patterns were

TABLE 2
Factors Not Significantly Related to Recurrence in Univariate Analysis

Factor	No. of patients	No. of recurrences (%)	P value
Grade of tumor			
Well/moderately differentiated	100	6 (6)	0.68
Poorly/undifferentiated	96	9 (9.3)	
Tumor growth pattern			
Exophytic	49	4 (8.1)	0.91
Endophytic	147	11 (7.5)	
Tumor stromal border			
Pushing	53	1 (1.9)	0.10
Tentacular	143	14 (9.8)	
Degree of necrosis in tumor			
Little/moderate	170	13 (7.6)	0.59
Extensive	26	2 (7.7)	
Stromal desmoplasia			
None/little	156	11 (7.1)	0.30
Extensive	40	4 (10)	
Stromal inflammatory cell infiltrate			
Light/moderate	123	7 (5.7)	0.06
Extensive	73	8 (11)	
Predominant inflammatory cell type			
Lymphocytes	176	13 (7.4)	0.73
Eosinophiles	20	2 (10)	
Vascular space invasion			
No	123	7 (5.7)	0.20
Yes	73	8 (11)	
Parametrium infiltration			
No	177	13 (7.3)	0.55
Yes	19	2 (10.5)	
Involvement of vagina			
No	180	13 (7.2)	0.46
Yes	16	2 (12.5)	
Stage			
IB	179	15 (8.4)	0.10
IIA	17	0 (0)	
Adjuvant radiotherapy			
No	170	13 (7.6)	0.99
Yes	26	2 (7.7)	

noted. The sites of recurrence were categorized as pelvic (recurrences involving the central pelvic region, such as the vagina, bladder and rectum, as well as those involving the pelvic sidewall) and distant (recurrences outside the pelvis). Except for one distant recurrence, all recurrences were histologically confirmed.

The original pathology slides from the study group were reviewed and the following pathologic characteristics evaluated: histologic tumor type, differentiation grade, tumor diameter, depth of invasion measured in millimeters from the basement membrane, depth of invasion as a fraction of cervical stroma penetration by the tumor (calculated as the depth of invasion in millimeters divided by the distance from the tumor's surface to the fibromuscular parametrial border), parametrium infiltration, vaginal involvement, tumor

TABLE 3
Significant Factors Selected by Cox Proportional Hazards Regression Analysis

Factor	Hazards ratio (95% CI)	P value
Adenocarcinoma	2.3 (1.3–4.0)	0.003
FCSP	4.6 (3.6–5.9) per one-third increase	0.01
SICI	2.5 (1.0–6.2) for an extensive response	0.04

CI: confidence interval; FCSP: fraction of cervical stroma penetration; SICI: stromal inflammatory cell infiltrate.

growth pattern (exophytic or endophytic), tumor stromal border (pushing or tentacular), vascular space invasion, host response (quality and quantity of the stromal inflammatory infiltrate and the degree of desmoplastic reaction of the stroma), and the degree of necrosis within the tumor.

Comparisons of groups were made using the chi-square test, Fisher's exact test, and Pearson's correlation coefficient (r). Disease free interval (DFI) was estimated by the Kaplan-Meier method.¹³ The log rank test was used to determine whether differences existed between the groups. Patients who died of intercurrent disease or who were lost to follow-up were censored at the time of last known follow-up. Multivariate analysis was performed using a Cox proportional hazards regression analysis in a forward stepwise manner; a P value of 0.05 was the criteria for inclusion.

RESULTS

The average age of the 196 patients was 44 years (range, 22–77 years). There were 158 patients with squamous cell carcinoma, 37 with adenocarcinoma (including 4 with adenosquamous carcinoma), and 1 with undifferentiated carcinoma. Adjuvant pelvic radiotherapy (40–50 gray in 4–5 weeks) was administered to 26 patients for the following reasons: parametrium infiltration ($N = 17$), spill during surgery ($N = 1$), close or involved margins ($N = 4$), or a combination of factors ($N = 4$). The median duration of follow-up for censored patients was 68 months. The estimated 5-year DFI for the entire group was 92%. Fifteen patients experienced recurrent disease (7.7%): 9 developed a pelvic recurrence (including 3 patients with a concomitant distant recurrence) and 6 a distant recurrence. Among the 26 patients who received adjuvant radiotherapy, 1 developed a pelvic recurrence and 1 a distant recurrence. A large number of surgical pathologic factors were subjected to univariate and multivariate analysis to determine whether they were associated

FIGURE 1. Disease free interval is shown according to the number of risk factors.

with recurrence. Some of these factors were found to be interrelated. For example, a significant correlation was found between tumor size and depth of invasion ($r = 0.63$, $P = 0.001$) and between tumor size and the fraction of cervical stroma penetration by the tumor ($r = 0.56$, $P = 0.001$).

The results of the univariate analysis with respect to DFI are presented in Table 1 (significant factors) and Table 2 (nonsignificant factors). Significant factors included adenocarcinoma, tumor size, depth of invasion in millimeters, and depth of invasion as a fraction of cervical penetration by the tumor.

When all factors were included in a Cox regression analysis for DFI, adenocarcinoma ($P = 0.003$), fraction of cervical stroma penetration ($P = 0.01$), and stromal inflammatory cell infiltrate ($P = 0.04$) were the only independent factors that were predictive of recurrence (Table 3). In the Cox model, the hazard increased by an estimated factor of 4.6 (95% confidence interval [CI]: 3.6–5.9) per one-third increase in the fraction of cervical stroma penetration. Patients with adenocarcinoma had an estimated 2.3 (95% CI: 1.3–4.0) times higher hazard than patients with squamous cell carcinoma. For the stromal inflammatory cell infiltrate factor, the hazard ratio was 2.5 (95% CI: 1.0–6.2) when there was an extensive response compared with a light or moderate response. Based on the hazard ratios, the following risk factors were defined: adenocarcinoma, extensive infiltrate stroma response, and cervical stroma penetration $\geq 2/3$. The 5-year DFI for patients without any risk factor was 97% (standard error [SE]: 2.5%), whereas for patients with one risk factor and patients with more than one risk factor, the DFIs were 98% (SE: 1.7%) and 81% (SE: 5.3%), respectively (Fig. 1). According to these figures, risk groups for DFI were formed as shown in Table 4. In the low risk group, 4 of 140 patients developed a recurrence (2.9%), whereas in the high risk group, 11 of 55 patients developed a

TABLE 4
Classification of Risk Groups Based on the Number of Independent Risk Factors (0–1 vs. >1)

No. of risk factors	Risk group	N	FCSP	Histology	SICI
0–1	Low risk	88	<2/3	SCC	Any
	Low risk	18	<2/3	AC	Light/moderate
	Low risk	34	≥2/3	SCC	Light/moderate
2–3	High risk	3	<2/3	AC	Extensive
	High risk	16	≥2/3	AC	Any
	High risk	36	≥2/3	SCC	Extensive

FCSP: fraction of cervical stroma penetration; SICI: stromal inflammatory cell infiltrate; AC: adenocarcinoma; SCC: squamous cell carcinoma.

TABLE 5
Recurrence Patterns for the Various Risk Groups

Risk group	Recurrence rate	Site of recurrence		
		Pelvic	Pelvic + distant	Distant
Low risk	4/140	1	2	1
High risk	11/55	5	1	5

recurrence (20%). The 5-year DFI for the low risk group was 97% (SE: 2.1%), compared with 81% (SE: 5.3%) for the high risk group. The recurrence patterns for the various risk groups are shown in Table 5. In the high risk group, there were five distant recurrences and six pelvic recurrences (including one with a concomitant distant recurrence).

To determine which pathologic factors influenced local tumor control, a Cox regression analysis for pelvic recurrence was performed using all previously mentioned pathologic factors. Adenocarcinoma ($P = 0.03$), fraction of cervical penetration ($P = 0.03$), and tentacular tumor stromal border ($P = 0.02$) proved to be independent factors.

DISCUSSION

In the current study, we attempted to identify risk factors for tumor recurrence among a group of 196 Stage IB and IIA cervical carcinoma patients with negative pelvic lymph nodes after radical hysterectomy. In multivariate analysis, the prognostic significance of a large number of surgical pathologic factors was determined.

In this analysis, adenocarcinoma was an independent risk factor for recurrence. In the literature, varying results have been reported with respect to the prognostic significance of tumor histology. In some multivariate studies, adenocarcinoma was found to be a poor prognostic factor,^{14,15} whereas in other studies, tumor histology had no influence on survival.^{5,16,17}

None of these studies, however, had focused on lymph node negative patients only. Fuller et al., on the other hand, separately analyzed 343 lymph node negative patients and found that by univariate analysis, patients with adenocarcinoma had a significantly decreased survival rate compared with squamous cell carcinoma patients.¹⁸ A similar observation was made by Burke et al.¹⁹ In a multivariate analysis of Stage IB lymph node negative patients, Hopkins et al. found that besides the fraction of cervical stroma penetration, adenocarcinoma was also an independent risk factor for survival.²⁰

Generally, tumor size is regarded as a major prognostic factor in early stage cervical carcinoma.^{5,21} However, as demonstrated in this study as well as in previous studies,¹⁸ tumor size is closely related to other variables associated with tumor volume, such as depth of invasion in absolute millimeters and as a fraction of cervical stroma penetration. In the current multivariate analysis, all these of three factors were included. Only for the fraction of cervical stroma penetration was evidence found of an association with recurrence. This suggests that the prognostic significance of tumor size and depth of invasion in millimeters, as observed in the univariate analysis, arose only in their association with the fraction of cervical stroma penetration. A possible explanation for these findings is that as a tumor involves a greater fraction of the cervical stroma, the risk for metastatic spread increases because the tumor gains more access to larger lymphatic trunks and blood vessels that insert at the periphery of the cervix. Because the fraction of cervical penetration depends not only on the depth of invasion but also on the thickness of the cervix, this ratio is different in an atrophic cervix than in a large, premenopausal, multiparous cervix, given an equal depth of tumor invasion.²² In a recent multivariate analysis in which tumor size and cervical penetration by the tumor were both included as variables, cervical

TABLE 6
Review of the Literature Addressing the Patterns of Recurrence in Patients with Early Stage Cervical Carcinoma and Negative Lymph Nodes Who Have Been Treated by Radical Surgery

Reference no.	Recurrence rate (%)	No. of recurrences			% Pelvic
		Pelvic	Pelvic + distant	Distant	
3	18/392 (5)	17	0	1	94
5	20/241 (8)	15	0	5	75
11	10/171 (6)	4	0	6	40
26	65/467 (14)	34	0	31	52
27	28/283 (10)	19	0	9	68
28	23/159 (14)	21	2	0	100
29 ^a	38/437 (9)	13	0	18	42
30	3/68 (4)	3	0	0	100
31	19/165 (12)	9	3	7	63
32	6/56 (11)	5	0	1	83
33	82/733 (11)	58	0	24	71
34	18/237 (8)	17	0	1	94
35	9/61 (15)	7	1	1	89
36	4/36 (11)	3	0	1	75
Current study	15/196 (8)	6	3	6	60
Total	358/3702 (10)	231	9	111	71

^a In 7 patients the site of recurrence was unknown.

penetration was an independent prognostic factor, whereas tumor size and pelvic lymph node metastases were not.²² The same authors performed the analysis on the group of lymph node negative patients only, and again cervical penetration had more prognostic significance than tumor size.²⁰ Delgado et al. demonstrated in a large study of the Gynecologic Oncology Group of the National Cancer Institute (GOG) that the risk of pelvic lymph node metastases for patients with Stage I disease was more strongly associated with depth of invasion in fractional thirds (as fractions of cervical penetration) than depth of invasion in absolute millimeters.²³ In another GOG report on Stage IB squamous carcinoma, it was found that the risk of recurrence in patients with tumors invading the outer third of the cervix was very high and not influenced by depth of invasion in absolute millimeters.²¹ In our opinion, these observations warrant further investigation to determine if depth of invasion as a fraction of cervical penetration is a more critical determinant for prognosis than depth of invasion in absolute millimeters or tumor size.

The degree of stromal inflammatory cell infiltrate was also a significant prognostic factor for recurrence in this study, although its association was less pronounced ($P = 0.04$). In the literature, only a few reports have investigated the prognostic significance of this factor in early stage cervical carcinoma.²⁴ Some authors noticed a better outcome when there was a predominance of eosinophilic leukocytes.²⁵ However, we

were unable to confirm this. We feel that the prognostic significance of this factor needs further clarification.

Based on these three independent prognostic factors, we were able to define a subgroup of 55 high risk patients that comprised 11 of the 15 recurrences. Because the factors adenocarcinoma and fraction of cervical stromal penetration were also significantly related to locoregional tumor control, this subgroup included 5 of the 6 isolated pelvic recurrences.

In the current study, the proportion of pelvic recurrences was 60% (9/15). Table 6 presents a review of the literature addressing the patterns of recurrence in surgically treated patients with early stage cervical carcinoma and negative pelvic lymph nodes. The collated data showed that in this category of patients, more than two-thirds of the recurrences were located in the pelvic region. This raised the question of whether local tumor control in such patients might be improved with adjuvant pelvic radiotherapy. Although the effect of adjuvant radiotherapy has never been determined in a prospective randomized trial, Kinney et al. provided data strongly suggesting that it is highly effective in preventing pelvic recurrences.³⁷ In their matched control study on lymph node positive patients, a 40% reduction in pelvic recurrences was observed with adjuvant pelvic radiotherapy. In non-matched retrospective studies, a similar observation was made.^{38,39}

In a retrospective, nonmatched study, Remy et al.

evaluated the value of adjuvant pelvic radiotherapy in a subset of Stage IB lymph node negative patients with deeply invasive tumors. The percentage of patients with a fraction of cervical stroma penetration $\geq 2/3$ was comparable between the irradiated and the nonirradiated patients. The pelvic recurrence rate in the irradiated group was 12%, compared with 22% in the nonirradiated group.³⁹ Vavra et al. also found in their retrospective analysis that lymph node negative patients who received adjuvant radiotherapy had better outcomes than those who were not irradiated.⁴⁰ In our study, the recurrence rate for patients who received adjuvant radiotherapy (N = 26) was comparable to that for nonirradiated patients: 7.7% (2/26) versus 7.8% (13/170). However, among the irradiated patients, 88% had tumors with a fraction of cervical stroma penetration $\geq 2/3$, compared with 37% among the nonirradiated patients ($P < 0.0001$).

Based on the data from the literature and the results of the current series, a prospective randomized trial that would investigate the value of adjuvant pelvic radiotherapy in selected lymph node negative patients seems warranted. Such a trial should at least include a subgroup of patients who are high risk (as defined in the current study). Regarding such a trial, there are some issues of concern that need consideration. Firstly, the current study shows that even in a high risk group, a considerable proportion of the patients remain disease free. For these patients, any kind of adjuvant therapy is an overtreatment that might increase morbidity. Second, there are a number of patients for whom improvement of local tumor control would not be beneficial because they would ultimately develop distant recurrences. It is unlikely, however, that these patients could be identified by pathologic findings. We await with great interest the results of a randomized trial conducted by the GOG that has investigated the value of adjuvant pelvic radiotherapy for selected Stage IB patients.

In conclusion, this study shows that in patients with early stage cervical carcinoma and negative lymph nodes, adenocarcinoma, deep cervical stroma penetration by the tumor, and an extensive stromal inflammatory cell infiltrate are significant risk factors for recurrence. Concordant with the literature, it was found that the majority of recurrences in the lymph node negative group were pelvic recurrences.

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