Surgical pathologic factors in patients with early-stage cervical carcinoma treated with radical hysterectomy and pelvic lymph node dissection: association with administration of adjuvant radiotherapy and effect on survival

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Summary

Purpose of investigation: To identify surgical pathologic factors that best correlate with administration of adjuvant radiotherapy and best predict survival in 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: Fifty-four percent of the patients received postoperative adjuvant radiotherapy. In a univariate analysis, each of the following factors: positive pelvic lymph nodes, lower uterine segment involvement, lymph vascular space involvement, penetration ≥ 50% of the cervical wall, grade 2+3, parametrial and/or paracervical involvement, vaginal margin involvement, non-squamous histologic type, tumor size ≥ 3 cm and Stage IB_2 + IIA was significantly associated with administration of radiotherapy. In a multivariate analysis, positiviy of pelvic lymph nodes was persistently the most significant factor associated with administration of radiotherapy. The 5-year survival rate was 82.6% overall. In a univariate analysis, a significant worsening in survival was demonstrated with positivity of pelvic lymph nodes and positivity of lymph vascular space involvement. In a "better fit" model of multivariate analysis, pelvic lymph node status was the strongest and the only significant predictor of survival.

Conclusions: In patients with early-stage cervical carcinoma treated with radical hysterectomy and pelvic lymph node dissection, pelvic lymph node status is the strongest factor affecting administration of adjuvant radiotherapy and the most significant predictor of survival.

Key words: Cervical carcinoma; Prognostic factors; Adjuvant radiotherapy; Survival.

Introduction

Primary therapy for early-stage cervical carcinoma (FIGO clinical Stage IA_2, IB_1, IB_2, and IIA) is either radical hysterectomy and pelvic lymph node dissection (RHND) or radiotherapy with external pelvic irradiation and brachytherapy [1-4]. Although these treatment modalities are equally efficacious with respect to survival, surgery is often preferred to radiotherapy in younger women because of the possibility of preserving the ovaries and the reduction in vaginal morbidity [1, 5-7]. Nevertheless, high-risk surgical pathologic factors such as positive pelvic lymph nodes, positive parametrial and/or paracervical involvement, positive vaginal margin involvement, tumor size ≥ 4 cm, penetration ≥ 50% of the thickness of the cervical wall, positive lymph vascular space invasion, close vaginal margins, 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 treated with RHND [7,8]. High-risk factors such as positive pelvic lymph nodes, parametrial and/or paracervical involvement and involved vaginal margins are considerably stronger than others in predicting adverse outcome; thus, they are often designated "hard" high-risk factors while the others are called "soft" high-risk factors (Table 1). In the presence of high-risk surgical pathologic 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]. However, the selection of specific prognostic factors that serve as indications for administration of adjuvant pelvic radiotherapy has yet not been well established [4, 6]. The policy in our institution has been that in the presence of at least one "hard" high-risk factor, or at least two "soft" high-risk factors, the administration of adjuvant pelvic radiotherapy is seriously considered. This study was performed to identify the surgical pathologic factors that best correlate with administration of adjuvant radiotherapy and best predict survival in patients with early-stage cervical carcinoma treated by RHND.

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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 and followed-up at the Soroka Medical Center, Beer-Sheva, Israel between January 1962 and October 2005 were reviewed. Notably, 122 (96.8%) of the 126 patients were treated between January 1981 and October 2005. The surgical technique performed of RHND was consistent with a Class III extended hysterectomy as described by Piver *et al.* [9]. The pelvic lymph node dissection consisted of removal of all lymphatic tissue around the common, external, and internal iliac vessels and anterior to the obturator nerve. For patients who received postoperative adjuvant pelvic radiotherapy, it consisted of external megavoltage photonic irradiation employing a 10 MeV linear accelerator usually delivering 4,500-5,040 cGy to the whole pelvis in daily fractions of 180 cGy via an AP-PA opposed fields or four-field box technique. This was usually followed by two vaginal intracavitary applications of brachytherapy using Cesium-137 (each application, 2,000 cGy) via a vaginal cylinder (Delclos) or ovoids (colpostats). Since January 2000, external pelvic radiotherapy was concomitantly given with intravenous chemotherapy composed of weekly cisplatin 40 mg/m^2. 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 [10]. The following data were retrieved from the files of the patients: age at diagnosis, menopausal status, parity, presenting symptoms, stage of disease, histopathological findings, application of postoperative adjuvant pelvic radiotherapy, and results of follow-up.

Differences between patient groups were tested by the chi-square test with Yates' correction for small numbers and/or the Fisher exact test [11]. Multivariate analysis with use of backward and forward stepwise logistic regression analysis [12] was conducted to evaluate the joint effects of surgical pathologic variables on administration of adjuvant radiotherapy. Survival was calculated using the Kaplan-Meier method [13] and compared statistically with use of the log-rank test [14]. Multivariate analysis with use of Cox proportional hazards regression analysis [15] was employed to evaluate the joint effects of surgical pathologic variables on survival. Only p values < 0.05 were considered statistically significant.

Results

Age at diagnosis ranged from 20 to 71 years (mean, 44.5 years). Eighty-seven (69%) patients were premenopausal and 39 (31%) were postmenopausal. Clinical stage of disease at the time of presentation was IA_1 in two (1.6%) patients, IA_2 – three (2.4%), IB_1 – 73 (57.9%), IB_2 – 31 (24.6%), IIA – 16 (12.7%), and not recorded – one (0.8%). Ninety-seven (77%) patients had squamous cell carcinoma, 12 (9.5%) – adenosquamous carcinoma, six (4.8%) – glassy cell carcinoma, five (3.9%) – adenocarcinoma, three (2.4%) – verrucous carcinoma, two (1.6%) – clear cell carcinoma and one (0.8%) – not known. Lower paraaortic lymphatic-fatty tissue sampling was performed during RHND in 58 (46%) patients. In 31 (53.5%) of these 58 patients, histologic examination detected at least one paraaortic lymph node (range 1-12 nodes). All paraaortic lymph nodes removed were negative for metastases. Information with respect to number and status of pelvic lymph nodes removed during RHND was available for 114 (90.5%) 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 114 patients. The mean number of positive pelvic lymph nodes per patient in patients with positive pelvic lymph nodes was 3.4 (median, 2; range 1-15).

Information with regard to administration of postoperative adjuvant pelvic radiotherapy was available for 124 patients; 67 (54%) received radiotherapy, 42 received external pelvic irradiation (XRT) followed by brachytherapy (BT), 14 received XRT alone and 11 had BT alone. With respect to the 56 patients who received XRT, the total dose of XRT per patient ranged from 3,600 cGy to 9,960 cGy (mean 4,734 cGy; median 4,500 cGy). With respect to the 53 patients who received BT, the total dose of BT per patient ranged from 500 cGy to 6,000 cGy (mean 2,683 cGy; median 2,100 cGy). Univariate analysis with use of the chi-square test with Yates' correction for small numbers demonstrated that each of the following factors: positive pelvic lymph nodes ($p < 0.0001$), positive lower uterine segment involvement ($p < 0.0001$), positive lymph vascular space involvement ($p = 0.001$), penetration $\geq 50\%$ of the thickness of the cervical wall ($p = 0.001$), grade 2+3 ($p = 0.002$), positive parametrial and/or paracervical involvement ($p = 0.004$), positive vaginal margin involvement ($p = 0.009$), histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell carcinoma ($p = 0.028$), tumor size ≥ 3 cm ($p = 0.028$) and Stage IB_2 + IIA ($p = 0.049$) was significantly associated with administration of adjuvant radiotherapy (Table 2). Notably, univariate analysis failed to demonstrate that tumor size ≥ 4 cm was significantly more associated with administration of adjuvant radiotherapy than tumor size < 4 cm ($p = 0.285$) (Table 2). Multivariate analysis (logistic regression) of all factors that were significantly associated with administration of adjuvant radiotherapy in the univariate analysis ("full or saturated model") demonstrated that only positive pelvic lymph nodes ($p < 0.0001$) and positive vaginal margin involvement ($p = 0.023$) were significantly asso-

Table 1. — *High-risk prognostic factors in early-stage cervical carcinoma treated with RHND.*

"Hard" high-risk factors
Involved pelvic lymph nodes*
Parametrial/paracervical involvement
Involvement of vaginal margins
"Soft" high-risk factors
Tumor size ≥ 4 cm
Penetration $\geq 50\%$ thickness of cervical wall.
Lymph/vascular space involvement (LVSI).
Close vaginal margins
Poor differentiation (G3).
Adenosquamous histologic type
Glassy cell histologic subtype
Clear cell histologic subtype

* In squamous cell carcinoma, at least three positive ipsilateral lymph nodes or at least one positive lymph node in each side. In non-squamous cell carcinoma, even if one lymph node only is involved.

Table 2. — *Univariate analysis of surgical pathologic factors in relation to administration of adjuvant radiotherapy in patients with early-stage cervical carcinoma treated with RHND.*

Factor	Number of patients	Adjuvant radiotherapy No (%)	Yes (%)	p value
Positive pelvic lymph nodes				
No	79	47 (59.5)	32 (40.5)	
Yes	35	4 (11.4)	31 (88.6)	< 0.0001
Lower uterine segment involvement				
No	85	48 (56.5)	37 (43.5)	
Yes	33	6 (18.2)	27 (81.8)	< 0.0001
Lymph vascular space invasion				
No	74	43 (58.1)	31 (41.9)	
Yes	44	11 (25.0)	33 (75.0)	0.001
Penetration of cervical wall				
< 50%	43	29 (67.4)	14 (32.6)	
≥ 50%	81	28 (34.6)	53 (65.4)	0.001
Grade				
1	27	20 (74.1)	7 (25.9)	
2+3	97	37 (38.1)	60 (61.9)	0.002
Parametrial/paracervical involvement				
No	89	48 (53.9)	41 (46.1)	
Yes	29	6 (20.7)	23 (79.3)	0.004
Vaginal margin involvement				
No	102	52 (51.0)	50 (49.0)	
Yes	16	2 (12.5)	14 (87.5)	0.009
Histologic type				
SCC	96	49 (51.1)	47 (48.9)	
AS, GC, AC and CC	25	6 (24.0)	19 (76.0)	0.028
Tumor size				
< 3 cm	49	29 (59.7)	20 (40.8)	
≥ 3 cm	75	28 (37.3)	47 (67.7)	0.028
Stage				
IA_2+IB_1	76	40 (52.6)	36 (47.4)	
IB_2+IIA	46	15 (32.6)	31 (67.4)	0.049
Tumor size				
< 4 cm	82	41 (50.0)	41 (50.0)	
≥ 4 cm	42	16 (38.1)	26 (61.9)	0.285

Note: Information regarding administration of adjuvant radiotherapy was available for 124 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 124.
SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

ciated with administration of adjuvant radiotherapy, whereas the association of histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell carcinoma with administration of adjuvant radiotherapy was of borderline significance (p = 0.052) (Table 3). After sequential elimination by backward stepwise logistic regression of non-significant factors from the initial saturated multivariate model, a "better fit" multivariate model was achieved that showed that the following factors: positive pelvic lymph nodes (p < 0.0001), penetration ≥ 50% of thickness of cervical wall (p = 0.013), positive vaginal margin involvement (p = 0.018) and histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell carcinoma (p = 0.032) were significantly associated with administration of adjuvant radiotherapy (Table 4).

Follow-up ranged from 5 to 528 months, with 56 (44.5%) of the 126 patients followed for at least five years or until time of death. At the end of follow-up, 103

Table 3. — *Multivariate analysis (logistic regression) of surgical pathologic factors with endpoint administration of adjuvant radiotherapy in patients with early-stage cervical carcinoma treated with RHND. This initial "full or saturated model" includes all factors that were significantly associated with administration of adjuvant radiotherapy in the univariate analysis.*

Factor	Odds Radio	95% confidence interval	p value
Positive pelvic lymph nodes			
No	1.000	Reference	
Yes	10.497	2.826-38.988	< 0.0001
Vaginal margin involvement			
No	1.000	Reference	
Yes	8.084	1.336-48.930	0.023
Histologic type			
SCC	1.000	Reference	
AS, GC, AC and CC	3.733	0.991-14.071	0.052
Penetration of cervical wall			
< 50%	1.000	Reference	
≥ 50%	2.258	0.697-7.318	0.174
Grade			
1	1.000	Reference	
2+3	2.409	0.659-8.812	0.184
Lower uterine segment involvement			
No	1.000	Reference	
Yes	2.724	0.537-13.806	0.226
Tumor size			
< 3 cm	1.000	Reference	
≥ 3 cm	1.598	0.548-4.656	0.390
Lymph vascular space invasion			
No	1.000	Reference	
Yes	1.162	0.346-3.902	0.808
Parametrial/paracervical involvement			
No	1.000	Reference	
Yes	0.851	0.184-3.933	0.836
Stage			
IA_2+IB_1	1.000	Reference	
IB_2+IIA	0.924	0.256-3.328	0.904

SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

Table 4. — *Multivariate analysis (logistic regression) of surgical pathologic factors with endpoint administration of radiotherapy in patients with early-stage cervical carcinoma treated with RHND. This "better fit" model was achieved after sequential removal of non-significant factors by backward stepwise logistic regression.*

Factor	Odds Radio	95% confidence interval	p value
Positive pelvic lymph nodes			
No	1.000	Reference	
Yes	10.917	3.204-37.191	< 0.0001
Penetration of cervical wall			
< 50%	1.000	Reference	
≥ 50%	3.599	1.310-9.887	0.013
Vaginal margin involvement			
No	1.000	Reference	
Yes	8.159	1.438-46.291	0.018
Histologic type			
SCC	1.000	Reference	
AS, GC, AC and CC	3.996	1.124-14.211	0.032
Grade			
1	1.000	Reference	
2+3	2.355	0.678-8.178	0.177

SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

Table 5. — *Univariate analysis with use of the log-rank test of surgical pathologic factors in relation to survival in patients with early-stage cervical carcinoma treated with RHND.*

Factor	Number of patients	5-year survival	p value
Positive pelvic lymph nodes			
No	79	90.99%	
Yes	35	60.25%	0.0001
Lymph vascular space invasion			
No	74	90.44%	
Yes	44	71.38%	0.0107
Penetration of cervical wall			
< 50%	43	91.84%	
≥ 50%	83	78.07%	0.0840
Tumor size			
< 4 cm	82	87.54%	
≥ 4 cm	44	73.85%	0.0896
Stage			
IA2+IB1	76	88.04%	
IB2+IIA	47	73.46%	0.1103
Parametrial/paracervical involvement			
No	89	85.88%	
Yes	29	44.63%	0.2235
Grade			
1	27	76.19%	
2+3	97	85.65%	0.3122
Radiotherapy			
No	57	86.13%	
Yes	67	80.83%	0.3969
Lower uterine segment involvement			
No	85	86.34%	
Yes	33	76.60%	0.4801
Vaginal margin involvement			
No	102	82.86%	
Yes	16	85.12%	0.7030
Histologic type			
SCC	97	82.04%	
AS, GC, AC and CC	25	81.80%	0.7466

Note: Information regarding survival was available for 126 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 126.
SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

(81.7%) patients were alive without disease, one (0.8%) was alive with disease, and 22 (17.5%) had died of disease. The actuarial 5-year survival rate was 82.6% overall. Univariate analysis with use of the log-rank test demonstrated a significant worsening in survival with positivity of pelvic lymph nodes (p = 0.0001) and positivity of lymph vascular space involvement (p = 0.0107), whereas penetration ≥ 50% of the thickness of the cervical wall (p = 0.0840) and tumor size ≥4 cm (p = 0.0896) were of borderline significance (Table 5). Multivariate analysis with use of Cox proportional hazards regression analysis of clinical and surgical pathologic variables with endpoint death demonstrated after sequential elimination by backward stepwise logistic regression of non-significant factors that pelvic lymph node status was the strongest and the only significant predictor of survival (p = 0.009) (Table 6).

Table 6. — *Multivariate analysis (Cox proportional hazards regression analysis) of clinical and surgical pathologic variables with endpoint death in patients with early-stage cervical carcinoma treated with RHND. This "better fit" model was achieved after sequential removal of non-significant factors by backward stepwise logistic regression.*

Factor	Number of patients	5-year survival	p value
Positive pelvic lymph nodes			
No	1.000	Reference	
Yes	4.435	1.454-13.523	0.009
Tumor size			
< 4 cm	1.000	Reference	
≥ 4 cm	1.860	0.666-5.192	0.236
Penetration of cervical wall			
< 50%	1.000	Reference	
≥ 50%	1.856	0.457-7.545	0.387
Lymph vascular space invasion			
No	1.000	Reference	
Yes	1.118	0.320-3.919	0.861

SCC, squamous cell carcinoma; AS, adenosquamous carcinoma; GC, glassy cell carcinoma; AC, adenocarcinoma; CC, clear cell carcinoma.

Discussion

High-risk surgical pathologic factors such as increased tumor size, virulent histologic type and poor differentiation are detected by cervical biopsy prior to surgery, whereas high-risk surgical pathologic factors such as positive pelvic lymph nodes and positive parametrial and/or paracervical involvement may be revealed at the start of surgery prior to the performance of RHND. Thus, one may challenge the wisdom of proceeding with the RHND if it is known in advance that high-risk surgical pathologic factors necessitating postoperative adjuvant pelvic radiotherapy are present [16, 17]. In other words, does the need for postoperative adjuvant pelvic radiotherapy because of the presence of high-risk surgical pathologic factors indicate that the RHND was superfluous? The answer is no. It has been observed that systematic pelvic lymphadenectomy in patients with positive pelvic lymph nodes increases survival [16, 18]. Furthermore, two studies have demonstrated that radiotherapy alone is unreliable in sterilizing bulky positive pelvic lymph nodes [19, 20]. It seems that bimodal therapy comprised of RHND followed by adjuvant pelvic radiotherapy is superior to either RHND alone or pelvic radiotherapy alone in improving the outcome of patients with high-risk early-stage cervical carcinoma [7, 16, 18, 21-24]. Moreover, the performance of RHND enables an accurate evaluation of tumor extension and, thus, a better tailoring of postoperative adjuvant radiotherapy [4, 6]. It is, however, generally agreed that RHND should be aborted if positive paraaortic lymph nodes are found at the start of surgery.

Pelvic lymphadenectomy during RHND should aim to remove all lymphatic fatty tissue around and between the major pelvic blood vessels and in the obturator fossa. In fact, the number of lymph nodes removed reflects the thoroughness of the procedure of RHND. In 1967, the FIGO stated that a systematic pelvic lymphadenectomy during RHND should remove at least 20 nodes from the whole pelvis [25, 26]. We have observed that the mean number of lymph nodes removed from the pelvis per patient was 26.6 and that 30.7% of the patients had positive pelvic lymph nodes with a mean of 3.4 positive pelvic lymph nodes per patient. 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 29.1%-55% of the patients had positive pelvic lymph nodes with a mean of 3.6 positive pelvic lymph nodes per patient [6, 21, 25, 27, 28].

By means of univariate analysis, we have observed that all high-risk surgical pathologic factors were significantly associated with administration of postoperative adjuvant radiotherapy, with positive pelvic lymph nodes and positive lower uterine segment involvement being the most significant factors. By means of multivariate analysis, with use of a "full or saturated model" that included all the factors that were significantly associated with administration of adjuvant radiotherapy in univariate analysis, we have demonstrated that only positive pelvic lymph nodes and positive vaginal margin involvement were significantly associated with administration of adjuvant radiotherapy. By means of multivariate analysis, with use of a "better fit" model achieved after sequential removal of non-significant factors by backward stepwise logistic regression, we have observed that positive pelvic lymph nodes, penetration ≥ 50% of thickness of cervical wall, positive vaginal margin involvement and histology type of adenosquamous carcinoma or glassy cell carcinoma or adenocarcinoma or clear cell carcinoma were significantly associated with administration of adjuvant radiotherapy. These findings corroborate other studies that demonstrated that positive pelvic lymph nodes is the most important high-risk factor associated with administration of postoperative adjuvant pelvic radiotherapy in patients with cervical carcinoma treated with RHND [1, 7, 8, 27]. It has generally been recommended that adjuvant pelvic radiotherapy after RHND for cervical squamous cell carcinoma should be given if more than three unilateral lymph nodes are involved or if one lymph node is involved in each side of the pelvis. In cervical adenocarcinoma, however, adjuvant pelvic radiotherapy has generally been recommended even if one unilateral lymph node is involved [29].

The actuarial 5-year survival rate in this series was 82.6% overall. By means of univariate analysis, we have observed a significant worsening in survival with positivity of pelvic lymph nodes and positivity of lymph vascular space involvement. By means of multivariate analysis, with use of a "better fit" model achieved after sequential removal of non-significant factors by backward stepwise logistic regression, we have demonstrated that pelvic lymph node status was the strongest and the only significant predictor of survival. These findings corroborate other studies that demonstrated that pelvic lymph node status is the strongest predictor of survival in patients with cervical carcinoma treated by RHND [5, 7, 23, 27]. In this study, the 5-year survival rate for patients with negative pelvic lymph nodes was 90.99%, whereas the 5-year survival rate for patients with positive pelvic lymph nodes was 60.25% ($p = 0.0001$). This is agreement with other studies that showed that patients with negative pelvic lymph nodes enjoy a 5-year survival rate of approximately 90%, whereas patients with positive pelvic lymph nodes have a 5-year survival rate ranging from 20% to 60% depending on the number of nodes involved, the location, and size of the metastases [5, 25, 27]. Burghardt [25] observed the following 5-year survival rates in relation to the number of positive pelvic lymph nodes: 0 – 89.3%, one – 69.8%, two-three – 62.1%, four – 36.9%. Inoue and Morita [27] showed the following 5-year survival rates in relation to the number of pelvic lymph nodes involved: 0 – 89%, one – 81%, two-three – 63%, four 18 – 41%, and unresectable positive lymph nodes – 23%. A 5-year survival rate of 25% was observed when the common iliac lymph nodes were positive, compared to a 5-year survival of 65% when the common iliac lymph nodes were negative and other pelvic lymph nodes only were involved [30]. Bilateral positive pelvic lymph nodes were associated with a significantly worse prognosis (5-year survival rate, 22%-40%) than unilateral positive pelvic lymph nodes (5-year survival rate, 59%-70%) [25, 30]. The survival of patients with microscopic invasion only of lymph nodes was better than that of patients with macroscopic lymph node metastases [30, 31]. By means of univariate analysis, Lin *et al.* [23] demonstrated that each of the following factors: histologic type of adenocarcinoma, bulky tumor size (> 4 cm), positive lymph vascular space invasion, deep cervical stromal invasion, and lymph node metastases was a significant risk factor for recurrence. In a multivariate analysis, bulky tumor size (> 4 cm), positive lymph vascular space invasion, and pelvic lymph node metastases remained significant risk factors [23]. Sevin *et al.* [28, 32] demonstrated by means of univariate analyses that significant worsening in survival was associated with increasing depth of invasion, increasing tumor size, involvement of lymph vascular spaces, positivity of pelvic lymph nodes, increasing tumor volume, and advancing clinical stage. Multivariate analysis demonstrated that depth of invasion, involvement of lymph vascular spaces, age, and status of pelvic lymph nodes were significant predictors of survival [28, 32]. In a univariate analysis, Kamura *et al.* [33] demonstrated that each of the following variables: pelvic lymph node status, histologic type, tumor size, degree of stromal invasion, lymph vascular space invasion and parametrial invasion was a significant predictor of survival. In a multivariate analysis, only pelvic lymph node status, histologic type and tumor size turned out to be significant prognostic factors [33].

Conclusion

Information on the status of surgical pathologic factors in early-stage cervical carcinoma treated with RHND is of utmost importance for making the decision of whether or not to administer postoperative adjuvant pelvic radiotherapy and for predicting survival. By means of univariate and multivariate analyses, we have demonstrated that positive pelvic lymph node status is persistently the strongest and most significant factor associated with administration of postoperative adjuvant pelvic radiotherapy. In a univariate analysis, a significant worsening in survival was demonstrated with positivity of pelvic

lymph nodes and positivity of lymph vascular space involvement. In a multivariate analysis, after achieving a "better fit" model, pelvic lymph nodes status was the strongest and the only significant predictor of survival.

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