Identifying local tumor variables for operable node-negative, margin-free patients with bulky cervical carcinoma of FIGO stage IB, IIA and IIB without adjuvant therapies

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Summary

Purpose: To identify local risk factors for FIGO IB, IIA and IIB bulky cervical squamous cell carcinoma (tumor size ≥ 4 cm) patients with node-negative, margin-free tumors treated by radical hysterectomy, pelvic lymph node and para-aortic lymph node dissections without adjuvant therapies.

Materials and methods: Thirty-four patients were recruited between 1976 and 1989 because they all declined any postoperative adjuvant therapy. The pathology reports showed that all the specimen margins were free from cancer cells with no para-aortic or pelvic lymph node metastases. The survival interval was calculated starting from the time of surgical intervention to the time of death or the end of this study in the year 2000.

Result: Tumor variables including cell differentiation, depth of stromal invasion, parametrial invasion, vaginal invasion, uterine body invasion, age, and FIGO stage were analyzed. Only vaginal invasion showed statistical significance for decreasing patient disease-free survival in both univariate and multivariate analyses with p values of 0.003 and 0.002, respectively.

Conclusion: For node-negative and margin-free patients with bulky cervical squamous cell carcinoma with operable stage IB and IIB, surgical intervention alone could suffice when no vaginal invasion is noted plus an 85% survival rate could be achieved. A prospective pilot study should be initiated although this study showed an excellent survival rate which is perhaps due to the limited number of cases.

Key words: Bulky tumor; Cervical neoplasm; Prognostic factors; Radical hysterectomy

Introduction

Bulky cervical cancer constitutes 10% of early stage cancer (Stage IB & II A) [1]. In the past, combinations of different modes of therapies were implemented with a negligible increase in overall 5-year survival rate and obviously increased morbidity compared to surgical intervention alone [2-7]. Until recently there have been studies showing clearly improved overall 5-year survival rate (around 85%) but significant morbidity could not be eradicated [8-10]. Therefore, this retrospective study was carried out to try to identify local tumor variables affecting the 5-year disease-specific survival rate of negative lymph-node and margin-free patients with operable bulky cervical squamous cell carcinoma. They all belonged to FIGO stage IB, IIA and IIB and refused to have any adjuvant therapies in any mode after radical hysterectomy and pelvic lymph node and para-aortic lymph node dissections.

Materials and Methods

From 1976 to 1989, 34 patients with bulky cervical squamous cell carcinoma were recruited in this study. The criteria were: (1) tumor size had to be greater or equal to 4 cm in any dimension; (2) all surgically resected pelvic and para-aortic lymph nodes had to be proven histologically negative for metastasis;

(3) all patients had to be surgically treated only; (4) only FIGO stages IB, IIA and IIB were included; (5) tumor cells belonged to the squamous cell type; and (6) all margins of the specimens had to be free from cancer cells. The survival interval was calculated starting with patients receiving surgical intervention to those either dying of the disease or alive and disease-free when this study finished in the year 2000. According to FIGO staging, 12 (35.30%) patients comprised stage IB, 16 (47%) patients comprised stage IIA and six (17.65%) patients comprised stage IIB. Specimens of all the 34 patients were obtained and their local pathological factors were assessed according to our previous experience [11-13]. These factors included lymphovascular space invasion, cell grade, depth of stromal invasion, vaginal invasion, parametrial invasion, and uterine body invasion. Age, staging and the above pathological factors were considered variables for statistical analysis in this study.

Survival curve was estimated by the Kaplan-Meier method. The Wilcoxon log-rank test was used to test differences in survival. The Cox proportional regression analysis was used in multivariate analysis with a p value of 0.05 as inclusion.

Results

Table 1 shows the variables mentioned above in relation to the 5-year disease-specific survival. Among these variables, only vaginal infiltration reached statistical significance in the Wilcoxon log-rank test with p = 0.003 in relation to differences in 5-year survival.

When all these variables were assessed in the Cox regression analysis, again vaginal infiltration was the

Table 1. — *Univariate Analysis of clinico-pathological variables.*

Variables	Number of patients	5-year disease-free survival rate	p value
Cell Grade			
I	11	81.80%	0.294
II, III	23	60.90%	
Depth of Stroma			
X ≤ 2/3	9	77.80%	0.444
X > 2/3	25	64.0%	
LVS Invasion			
Negative	21	61.90%	0.396
Positive	13	76.90%	
Vaginal Invasion			
Negative	21	85.70%	0.003
Positive	13	38.50%	
Parametrium Invasion			
Negative	21	66.70%	0.914
Positive	13	69.20%	
Uterine Body Invasion			
Negative	29	72.40%	0.227
Positive	5	40.0%	
FIGO Stage			
IB, IIA	28	71.40%	0.346
IIB	6	50.0%	
Age			
≤ 40 yrs old	6	66.70%	0.915
> 40 yrs old	28	67.90%	

only variable reaching statistical significance with p = 0.002. Table 2 shows the p value and confidence interval of each variable in the Cox regression analysis. Based on this factor, these 34 patients could be divided into a low-risk group and a high-risk group. The low-risk group comprised 21 patients and the high-risk group 13 patients. The 5-year disease-specific survival rates were 85.70 for the low-risk and 38.50% for the high-risk groups, respectively.

In our study, 11 patients (32.35%) had recurrences. Table 3 presents the site of recurrence of each patient. Eight patients (72.72%) had loco-regional recurrences and three patients (27.27%) had distant metastases. For the low-risk patients, three patients (14.28%) had recurrences with two having distant metastases and one loco-regional recurrence. The high-risk patients had eight members (61.53%) with recurrences (1 belonging to distant metastasis and 7 to loco-regional recurrences). However all these patients died within three years once recurrence was noted and none recurred retroperitoneally.

Table 2. — *Multivariate analysis of clinico-pathological variables.*

Variables	Relative Risk	S E	95% confidence interval	p value
Cell grade II, III/ I	1.164	0.939	0.185-7.328	0.872
Depth of stromal invasion				
X > 2/3/ X ≤ 2/3	9.615	0.791	0.810-111.111	0.073
LVS Invasion (+)/(-)	2.094	0.860	0.389-11.290	0.390
Vaginal invasion (+)/(-)	14.123	0.852	2.658-75.047	0.002
Parametrial invasion (+)/(-)	0.278	1.141	0.030-2.607	0.262
Uterine body invasion				
(+)/(-)	3.829	1.199	0.365-40.157	0.263
FIGO Stage IIB/IB, IIA	4.256	1.137	0.459-39.487	0.203
Age > 40 yrs. / < 40 yrs.	4.759	1.026	0.642-35.808	0.126

LVS = Lympho-vascular space.

Table 3. — *Site of recurrence in the risk groups.*

Risk Group	Number of patients	Number of recurrences	Site of Recurrence Loco-Regional (pelvis)	Distant
Low Risk Group				
Absence of vaginal invasion	21	3 (14.28%)	1	2
High Risk Group				
Presence of vaginal invasion	13	8 (61.53%)	7	1

Discussion

Presence of metastatic lymph nodes, regardless of the numbers found, masked the prognostic values of local tumor variables of every FIGO stage [11, 12, 14, 15] and guided this study to exclude patients with positive lymph nodes. We included only tumor sizes equal or greater to 4 cm in this study up to operable stage IIB due to (1) a watershed difference in 5-year survival rate in operable early stages [16, 17], (2) picking up tumor variables which effected differences in 5-year survival rates in this group of operable patients without further adjuvant therapies, and (3) finding out if the feasibility of surgical intervention alone could cure them based on this study when considering various modes of therapies presently proposed to treat operable bulky cervical cancer.

It was to our surprise that all the traditional adverse prognostic factors frequently mentioned in many studies did not apply to this study. Cell grade, reported by Fuller, *et al.* [16], did not show any statistical significance in this study. Our study did concur with a study reported by Delgado, *et al.* [18] but disagreed with a study done by Grimard, *et al.* [19] regarding invasion of the uterine body which did not reach statistical significance but showed clinical significance only. As for parametrial infiltration, no adverse effects in patient survival rate, both for FIGO stage as well as surgical stage were found when compared with previous studies [16, 18], whether lymph node metastasis was included or not. Age was also not noted to be a prognostic factor and thus did not concur with the reports done by Fuller, *et al.* and Alvarez, *et al.* [14, 15] but did agree with the study reported by Finan *et al.* [4] which showed age to not be significant, whether patients were node positive or not and whether the tumor size was bulky or not. In our study, FIGO stage IIA did not have as prominent an adverse effect as did surgical stage IIA because (1) Out of the 13 patients with pathologically-proven vaginal infiltration, only six of the 13 patients belonged to FIGO stage IIA; (2) Grouping of FIGO stage IB and IIA together could have shown and strengthened our tenet that parametrial invasion is not an adverse factor as traditionally believed, but could, on the other hand, have a diluting effect on its influence as an adverse factor; (3) A further diluting effect occurred when another five patients presenting with vaginal invasion went to FIGO stage IIB. Fuller, *et al.*, reported that depth of stromal invasion, especially cases belonging to the outer 1/3, had a poor prognosis when patients had both negative lymph nodes and bulky tumor and vaginal

invasion was not an adverse factor [16]. However, our study was the other way around with a p value = 0.002, which was significant for the presence of vaginal invasion according to Cox's proportional regression analysis. We did not find a statistical difference in disease-free survival whether the depth of stromal invasion was no less than 2/3 thickness or not. Our study also disagreed with studies [16, 18] showing that lympho-vascular invasion was a predictor of recurrence when lymph nodes were negative for metastasis. We did not agree with the report by Sedlis et al. [20] who put every node-negative patient with bulky cervical carcinoma on adjuvant pelvic radiotherapy after surgical intervention because (1) Our results showed that patients in the low-risk group had a similar overall 5-year survival rate when treated surgically alone with obviously less morbidity; (2) The majority (66.6%) of the low-risk patients had recurrences in distant sites which could not be reached by pelvic radiotherapy alone. Low-risk patients in our study, even with bulky tumor, stromal invasion, no adjuvant radiotherapy and invasion at least greater than 2/3 in depth, achieved a similar 5-year disease-specific survival rate as reported by Matsuyama, et al. [21]. Therefore our study did not support the conclusion that "Whether the malignant lesion involved the vaginal fornix or not reflected the size of the tumor and added no additional prognostic information" as far as bulky tumor was concerned [22]. Our study implied that the time needed for the malignant tumor to become bulky could allow conversion of the so-called cancer-induced vaginal cancer stage 0 into stage I or even higher stages, thus leading to the lower survival rate noted once the vagina was involved. We found a *recent* report by Boronow on the topic of the bulky 6-cm barrel-shaped lesion of the cervix: primary surgery and postoperative chemoradiation interesting [23]. In the high-risk group of patients, based on this study, immediate postoperative chemoradiation might have been beneficial.

In conclusion, meticulous selection of patients with bulky cervical carcinoma who undergo surgical intervention only might also achieve a similar survival rate to those who have adjuvant therapy with decreased morbidity. Due to the limited number of cases in our study, a prospective pilot study should be initiated.

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