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Pulmonary Metastasectomy for Uterine Cervical Cancer: A Multivariate Analysis

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Background. This study evaluated the results of resection of pulmonary metastases from cervical cancer.

Methods. A total of 7,748 patients with primary stage Ib or II cervical cancer underwent curative initial treatment consisting of radical hysterectomy or radiotherapy in 22 hospitals. Of the 7,748 patients, 29 (0.37%) patients had pulmonary metastases, which were detected after a disease-free period after initial treatment (radical hysterectomy or radiotherapy) and were resected with the intention to cure by June 30, 1998.

Results. The 5-year disease-free survival rate after pulmonary metastasectomy for all patients was 32.9%. Patients with one or two pulmonary metastases had a 5-year disease-free survival rate of 42.2% compared with 0% for patients with three or four metastases ($p = 0.0003$).

Patients with squamous cell cancers had a 5-year disease-free survival rate of 47.4% compared with 0% for patients with adenosquamous cell cancers or adenocarcinoma ($p = 0.0141$). On multivariate analysis, the significant prognostic variables for disease-free survival were two or fewer metastases ($p = 0.0232$) and squamous cell cancer ($p = 0.0168$).

Conclusions. Cervical cancer patients with pulmonary metastases after initial treatment (radical hysterectomy or radiotherapy) could expect to achieve long-term disease-free survival by pulmonary metastasectomy when there are two or fewer metastases diagnosed as squamous cell cancer.

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Although the prevalence of invasive cervical cancer among Japanese women has been reported to be gradually decreasing, new cases are still being diagnosed in approximately 7,000 women annually, and 60% of these women have progressive disease [1]. Overall, recurrent disease will develop in 10% to 20% of patients after primary radical surgery. The prognosis of recurrent cervical cancer is dismal. Thus, increasing our understanding of recurrence and treatment remains important.

Material and Methods

The stage of the disease was classified according to the criteria of the International Federation of Gynecology and Obstetrics.

A total of 7,748 patients with primary International Federation of Gynecology and Obstetrics stage Ib or II cervical cancer underwent initial treatment consisting of radical hysterectomy or radiotherapy in 22 hospitals between January 1, 1983, and December 31, 1997. All patients received potentially curative treatment consisting of radical hysterectomy or radiotherapy. Of the 7,748 patients, 29 (0.37%) patients had pulmonary metastases,

which were confirmed by chest radiography or computed tomography after a disease-free period after initial treatment (radical hysterectomy or radiotherapy) and were resected with the intention to cure by June 30, 1998. These patients were examined to analyze the prognostic factors for survival after pulmonary metastasectomy. Their metastatic disease was limited to the lungs.

All thoracotomy specimens were processed according to standard procedures for hematoxylin and eosin-stained histologic preparation and were histologically confirmed to contain cancer consistent with cervical cancer origin. Pulmonary metastases were completely resected in all patients. There were no operative or hospital deaths. Of the 29 patients, 15 patients received cisplatin-based chemotherapy as adjuvant treatment after pulmonary metastasectomy whereas the remainder had no other therapy. The median follow-up period of all patients was 40.1 months, and the median follow-up period of living patients was 51 months (range, 1.4 to 122.3 months).

Clinical data and follow-up information were obtained from the medical records and were further complemented using telephone contacts with patients, family members, and physicians. Disease-free survival (DFS) was defined as the elapsed time from thoracotomy to disease recurrence or death. Death from disease or any recurrent disease, local or distant, was considered an event in DFS calculation. Actuarial survival curves were calculated according to the Kaplan-Meier method [2], and comparisons were made

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with the log rank test [3]. For multivariate analysis, we used the Cox proportional hazards model. A *p* value of less than 0.05 was considered significant.

Results

Patients' Characteristics of Primary Cervical Cancer

The median age was 57 years, with a range of 31 to 76 years. There were 12 patients with stage Ib, 5 with stage IIa, and 12 with stage IIb disease. The histologic classification was made in accordance with the World Health Organization classification. Twenty patients had squamous cell cancers, 3 had adenosquamous cell cancers, and 6 had adenocarcinoma. All patients received potentially curative treatment of radical hysterectomy or radiotherapy. As initial treatment, 25 patients underwent radical hysterectomy and the remainder received radiotherapy. Of the 25 patients who underwent surgery, 8 patients had pelvic lymph node involvement. Four patients who had radiotherapy were not assessable.

Patients' Characteristics of Pulmonary Metastatic Lesions

The median age was 60 years, with a range of 32 to 77 years. The median disease-free interval (DFI, interval between initial treatment and onset of pulmonary metastasis) was 42 months (range, 11 to 97 months). A solitary metastatic lesion was found in 17 patients. Multiple metastases were found in the other 12 patients, two metastatic lesions in 6 patients, three metastatic lesions in 3 patients, and four metastatic lesions in 3 patients. In patients with a solitary metastasis, left lung metastasis was found in 5 patients, and right lung metastasis in 12 patients. In patients with multiple metastases, left lung metastases were found in 2 patients, right lung metastases in 3 patients, and metastases to both lungs in 7 patients. Wedge resection was performed in 8 patients (3 with a solitary lesion, 1 with two lesions, 2 with three lesions, and 2 with four lesions), segmentectomy in 2 patients (1 with a solitary lesion and 1 with four lesions), and lobectomy in 19 patients (13 with a solitary lesion, 5 with two lesions, 1 with three lesions). Median sternotomy was performed in 6 patients (3 with two lesions, 1 with three lesions, and 2 with four lesions), and lateral thoracotomy in 23 patients (17 with a solitary lesion, 3 with two lesions, 2 with three lesions, and 1 with four lesions). Sixteen patients underwent either hilar or mediastinal lymph node dissection. Of 11 patients who showed no evidence of any lymph node metastasis, 5 (45.5%) patients had postthoracotomy recurrence. However, of 5 patients who had hilar or mediastinal lymph node metastasis, 4 (80.0%) patients had postthoracotomy recurrence. Pulmonary metastatic tumor size was obtained in only 18 patients. Of 11 patients with pulmonary metastatic lesions less than 3 cm, 5 (45.5%) patients had postthoracotomy recurrence, and of 7 patients with pulmonary metastatic lesions more than 3 cm, 4 (57.1%) patients had postthoracotomy recurrence.

Table 1. Prognostic Factors: Estimation by Univariate Analysis

Factor	Number	5-year DFS Rate (%)	<i>p</i> Value
Stage			
Ib, IIa	17	34.1	0.9379
IIb	12	30.0	
Histology			
Squamous	20	47.4	0.0141
Adenosquamous + adeno	9	0	
Lymph node metastasis			
Positive	8	37.5	0.9414
Negative	17	25.3	
Age			
<60	13	15.4	0.0071
≥60	16	50.3	
DFI			
<36 months	10	30.0	0.3728
≥36 months	19	33.9	
Number of metastases			
1, 2	23	42.2	0.0003
3, 4	6	0	
Postthoracotomy chemotherapy			
Done	15	28.6	0.8146
None	14	38.1	

adeno = adenocarcinoma; DFI = disease-free interval; DFS = disease-free survival.

Univariate Analysis

The 5-year DFS rate after pulmonary metastasectomy for all patients was 32.9%. Table 1 summarizes the 5-year DFS rate and the results of the univariate analysis of the clinical and pathologic factors using the log rank test. Significant prognostic factors affecting DFS were histology (*p* = 0.0141), age (*p* = 0.0071), and number of metastases (*p* = 0.0003).

Multivariate Analysis

We performed multivariate analysis to identify independent factors affecting DFS. Number of metastases, age, histology, and DFI were included in the model. The results showed that the number of metastases (*p* = 0.0232) and the histology (*p* = 0.0168) were the only independent factors affecting DFS (Table 2). None of the other characteristics were significant on multivariate analysis. The actuarial 5-year DFS rates were 42.2% and 0% for patients with two or fewer metastases and those with three or four, respectively (Fig 1). Regarding histology, the actuarial 5-year DFS rates were 47.4% and 0% for patients with squamous cell cancers and adenosquamous cell cancers or adenocarcinoma, respectively (Fig 2).

Comment

Historically, patients who developed distant metastases from cervical cancer had a poor prognosis and were not considered for resection. Systemic treatment with chemo-

Table 2. Univariate and Multivariate Analysis

Factor	Univariate p Value	Multivariate		
		Hazard Rate	95% CI	p Value
Number of metastasis, 1, 2; 3, 4	0.0003	4.102	1.213-13.869	0.0232
Age, <60 y; ≥60 y	0.0071	0.382	0.126-1.163	0.0903
Histology, squamous; adsq + adeno	0.0141	3.775	1.271-11.212	0.0168
DFI, <36 months; ≥36 months	0.3728	0.662	0.232-1.891	0.4416

adeno = adenocarcinoma; adsq = adenosquamous cell cancer; CI = confidence interval; DFI = disease-free interval.

therapy is the mainstay of treatment for metastatic pulmonary tumors. Various chemotherapy regimens have been used to date. Imachi and associates [4] showed a 45% response rate in patients treated with two or more courses of chemotherapy; however, the mean interval from diagnosis of pulmonary metastasis to death was 7 months (median, 3 months; range, 1 to 59 months). The chemotherapy responses increased with the more frequent inclusion of platinum, but none of these regimens has proven to be useful in significantly prolonging survival [4, 5].

The 5-year DFS rate after pulmonary metastasectomy for the cervical cancer patients in our series was 32.9%, supporting the role of pulmonary resection in selected patients with pulmonary metastases from cervical cancer. The modified indications for pulmonary metastasectomy, ie, (1) the ability to tolerate the procedure, (2) sufficient pulmonary reserve to compensate for the loss of lung capacity, (3) the site of primary must be controlled or controllable, (4) no evidence of extrapulmonary disease, and (5) no better therapy available, are almost universally accepted [6-9]. We also have conformed to these criteria. The reported incidence of pulmonary metastasis from cervical cancer ranges from 2.1% to 9.1% [10-13]. Our 0.37% rate of lung involvement is lower than rates reported previously. This difference may be because we selected patients with stage Ib or II cervical cancer in whom pulmonary metastasis was detected after the disease-free period after initial treatment and surgery was performed in accordance with the indications for surgery described above. Our 65.5% incidence of lobectomy is higher than most pulmonary metastasectomy series. This

was for anatomic reasons, because there were many patients whose pulmonary metastatic lesions were near the hilum of the lung.

Five-year survival after pulmonary metastasectomy for cervical cancer varies greatly, ranging from 0% to 60% in some reports [6, 8, 14-17], because the indications and surgical methods differed. Some authors also have reported various factors affecting the survival after thoracotomy.

In this study, we investigated the stage, histologic type, presence or absence of pelvic lymph node metastasis, age, interval between initial treatment and pulmonary metastasis (DFI), number of metastatic pulmonary foci, and presence or absence of chemotherapy after resection as prognostic factors after resection of metastatic pulmonary foci. Univariate analysis showed that significant prognostic factors included the histologic type, age, and number of metastatic foci. On multivariate analysis, significant prognostic factors included the number of metastatic foci and histologic type.

Concerning histology, squamous cell carcinoma showed a better prognosis than adenosquamous cell carcinoma and adenocarcinoma on both univariate and multivariate analysis in our series. Imachi and colleagues [4, 18] reported that in patients with adenocarcinoma, the incidence of pulmonary metastasis and positive peritoneal cytology were higher than those in patients with squamous cell carcinoma, and that these findings were related to a poor prognosis.

With respect to pelvic lymph node metastasis, in our results, the presence or absence of pelvic lymph node

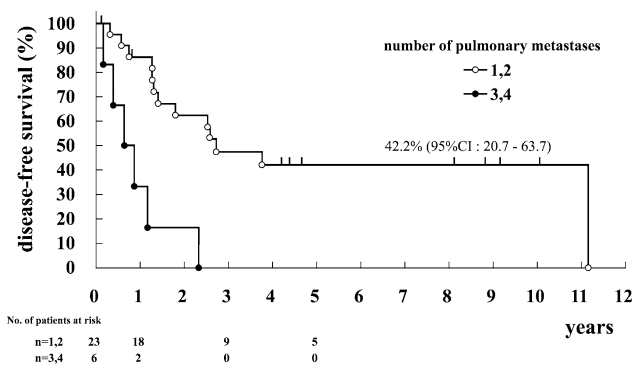


Fig 1. Disease-free survival, patients with one or two pulmonary metastases compared with those with three or four. (CI = confidence interval.)

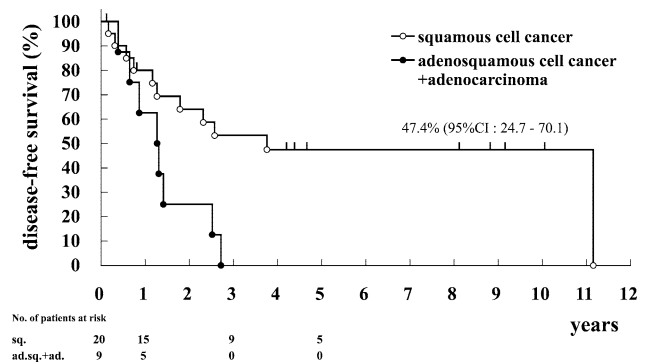


Fig 2. Disease-free survival, patients with squamous cell cancer compared with those with adenosquamous cell cancer or adenocarcinoma. (ad.sq.+ad. = adenosquamous cell cancer + adenocarcinoma; CI = confidence interval; Sq. = squamous cell cancer.)

metastasis did not influence the 5-year DFS. Shiromizu and coworkers [14] reported that patients with pulmonary metastasis alone without pelvic lymph node metastasis showed a good prognosis. However, treatment for metastatic pulmonary foci does not consist of surgery alone, and their subjects included patients with metastatic foci in organs other than the lungs. These factors may have contributed to the difference in results.

Our results showed that DFI did not significantly influence 5-year DFS. Barter and associates [5] reported that the interval between cancer diagnosis and onset of lung metastasis was not prognostic in cervical cancer. Seki and colleagues [16] reported that there were no significant differences between DFIs. However, Anderson and coworkers [10] reported that comparing DFI and survival, there were trends toward increased survival with greater DFI in patients with uterine cancer. Fuller and associates [19] reported that a prolonged time to initial recurrence (latent period) greater than 36 months was associated with improved survival and that there was a 60% survival among patients with latent periods of 60 months or more. Takita and coworkers [20] reported that for many malignancies, the interval between the initial diagnosis and the onset of lung metastasis is prognostic in surgically treated patients. However, that series involved not only cervical cancer but also other sites.

On univariate and multivariate analyses in our series, patients with one or two metastatic pulmonary foci showed a higher 5-year DFS than patients with three or four metastatic pulmonary foci. With respect to overall 5-year survival, Seki and colleagues [16] reported that there were no significant differences in the survival curves between the solitary and the multiple metastasis group.

There are no previous studies that have evaluated surgical therapy only in patients with stage Ib or II cervical cancer in whom pulmonary metastasis was detected after the disease-free period after initial treatment and resection was performed, as determined in this study. The results of this study may provide important information for future surgical therapy for pulmonary metastasis from cervical cancer.

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