Detection and Significance of Parametrial Micrometastases in Early-stage Cervical Cancer

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Abstract. Background: Parametrial metastases are rare in women with small, node-negative cervical tumors. We examined the incidence of micrometastases in women with pathologically negative parametria. Patients and Methods: Patients with IA-IB cervical cancer who underwent radical hysterectomy and had no evidence of parametrial metastases were examined. Immunohistochemistry (IHC) using a cytokeratin antibody was performed in parametrial sections. Results: Among 46 patients, a parametrial micrometastasis was identified in 1 (2.2%). Micrometastases were seen in 5% of women with lymphovascular space invasion (LVSI) and in 0 (0%) patients without LVSI (p=0.43). The patient with a parametrial micrometastasis experienced recurrence and died from her disease. In a previous report, we defined patients with tumors <2 cm, negative pelvic lymph nodes, and no LVSI as being at low-risk for parametrial disease. There were no micrometastases in this group of women in the current series. Conclusion: Parametrial micrometastases are uncommon in early-stage cervical cancer.

In 2008, it is estimated that 11,070 women were diagnosed with cervical cancer and that 3,870 died from their disease (13). Worldwide, nearly 500,000 cases of cervical cancer are diagnosed annually (27). Treatment for stage IA-IIA cervical cancer typically consists of either radical hysterectomy or radiation. A randomized clinical trial demonstrated equivalent survival for the two modalities (18).

Type III Wertheim radical hysterectomy consists of en bloc resection of the uterus, upper vagina, uterosacral ligaments and parametrium (29). While associated with excellent oncologic outcomes, the operation is also accompanied by significant morbidity (15, 19, 21, 28, 30). Nearly 40% of patients who underwent radical hysterectomy in a prospective trial had late morbidity associated with the procedure, including urologic complications in a third of patients (19). Much of the morbidity associated with the procedure stems from removal of the parametrial soft tissue (11). The autonomic nervous fibers, which play a critical role in normal voiding and sexual function, course through the parametrium and are susceptible to damage during parametrial resection performed at the time of radical hysterectomy.

The goal of parametrectomy is the resection of occult parametrial disease. However, the utility of radical parametrial resection has been questioned by a number of investigators (10, 22). The risk of parametrial metastasis appears to be small in women with early, small volume cervical tumors with favorable pathologic features (6, 16, 33). While parametrial metastases are rare in some subgroups of patients, the risk of occult micrometastasis is poorly understood. To date, relatively little work has been performed to examine the frequency of parametrial micrometastases in women with early-stage cervical cancer.

The goal of this study was to identify the frequency of parametrial micrometastases in women with early-stage cervical who had undergone radical hysterectomy and had no evidence of parametrial disease by standard pathologic analysis.

Patients and Methods

Study approval was obtained from the Columbia University Institutional Review Board. Patients with stage IA2-IIA cervical cancer who underwent type III radical hysterectomy as described by Piver et al. (29) between 1998 and 2007 were then examined. Only patients with negative parametria were included in the analysis. Demographic, clinical and pathologic data was abstracted from medical records. Disease status and vital status were obtained from a prospectively maintained hospital database.
All radical hysterectomy specimens were collected and processed in a routine clinical manner. Briefly, at the time of hysterectomy the parametrium and margins were inked for processing. The parametrial tissue was removed and processed separately. For the present study archival blocks of the parametrium were obtained and representative sections re-cut. Pathologic data reviewed included histology, grade, depth of tumor invasion, lymphovascular space invasion, vaginal and uterine involvement, pelvic and para-aortic lymph node status and status of the margins of excision.

Immunohistochemistry was performed on the re-cut parametrial sections of each patient. Two 5 µm slides were examined for each patient. Standard immunohistochemistry was performed using a mouse monoclonal anti-AE1/AE3 cytokeratin antibody at a dilution of 1:50 (Dako Corporation, Carpinteria, CA, USA). Each slide was examined by a gynecologic pathologist blinded to all patient data. A micrometastatic lesion was defined as a tumor implant between 0.2 mm and 2 mm.

Statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, N.C., USA). Patients who were alive were censored at the date of last contact. Overall survival was defined as the interval from surgery to death from any cause, and disease-free survival was defined as the time interval from surgery to the first incidence of recurrence or death, whichever occurred first. Those patients alive without recurrence were censored at the date of last contact. The association between parametrial micrometastases and other pathologic factors was evaluated using Fisher’s exact test. A p-value less than 0.05 was taken to indicate statistical significance and all tests were two-sided.

Results

Forty-six women with pathologically negative parametria at the time of radical hysterectomy were identified. The demographic and pathologic characteristics of the cohort are displayed in Table I. The median age of the patients was 42 years. Stage IB tumors were noted in 87% of patients, while 13% had stage IA lesions. Squamous histology predominated and the majority of tumors were <4 cm in diameter (65%). Lymphovascular space invasion was seen in 43% of the tumors. Eleven percent of women had pelvic nodal metastases, and 2% had para-aortic spread.

Parametrial micrometastasis was identified in 1 (2%) patient by immunohistochemistry. The micrometastasis was detected in a lymphvascular channel of the parametrium. The patient with a parametrial micrometastasis had a 3 cm adenocarcinoma with lymphvascular space invasion and no evidence of lymph node metastases. After initial treatment the experienced recurrence and died of disease.

The pathologic characteristics and outcomes between patients with and without parametrial micrometastases were then compared (Table II). None of the patients with stage IA tumors had parametrial micrometastases, while 3% of patients with IB tumors had microscopic parametrial disease (p=0.87). Likewise, parametrial micrometastases were not identified in any patients without lymphvascular space invasion but were found in 5% of those women with lymphvascular space invasion in the cervix (p=0.43).

Microscopic parametrial spread was seen in 6% of women with adenocarcinomas, and in no patients with squamous cell carcinomas (p=0.54). There was no apparent association between pelvic or para-aortic nodal spread and microscopic parametrial disease.

Recurrent or progressive disease was identified in 7% of patients without parametrial micrometastases and in the one patient with microscopic parametrial involvement (p=0.17). At the last follow-up, 4% of the women with negative immunohistochemistry and the one patient with parametrial micrometastases had died from their tumors (p=0.10).

Discussion

Our study demonstrates that parametrial micrometastases are uncommon in women with negative parametria by standard pathologic analysis. We were able to identify micrometastases to the parametrium in only 2% of our cohort. Given the rarity of parametrial micrometastases, it is difficult to determine the prognostic significance of the finding.

The identification of micrometastatic tumor deposits by immunohistochemistry has been successfully demonstrated for a number of solid tumors (1, 5, 7, 14, 17, 20, 23, 24, 26, 31). In cervical cancer, the concept has been most widely applied to the detection of occult lymph nodal metastases in women without nodal disease by standard analysis (20, 31). Among 132 patients with early-stage cervical cancer, Lentz and colleagues found micrometastases in 15% of the sentinel lymph nodes that were negative by standard hematoxylin and eosin analysis. The investigators proposed that this rate of micrometastases approximated the recurrence rate of node-negative cervical cancer, but they were unable to demonstrate an association between micrometastatic disease and tumor size or lymphvascular space invasion (20). In contrast, in a study of 49 early stage cervical cancer patients, Juretzka and co-workers found micrometastases in the pelvic lymph nodes of 8% of patients, and correlated micrometastasis to lymphovascular space invasion and tumor size (14). Despite the documentation of nodal micrometastases, the prognostic significance of this finding is uncertain. Marchiolle et al. found that in 292 patients with early-stage cervical cancer, while immunohistochemistry was not significantly more effective in determining micrometastasis to lymph nodes, the presence of these tumors was correlated to recurrence (23). A literature review examining micrometastases in gynecologic cancers concluded that the prognostic significance of microscopic metastases could not be determined from the body of literature currently available (7).

The present study focused specifically on the examination of the parametrial soft tissue for occult micrometastases. A recent report of 18 patients with negative parametria by standard histology noted parametrial micrometastases in 17% of patients. The researchers were unable to correlate microscopic parametrial involvement with outcome (4). The
rate of microscopic parametrial infiltration was lower in our study, only 2%. Similarly, however, we were unable to correlate parametrial micrometastatic disease with outcome or any specific pathologic characteristic. It is notable that in our series, microscopic parametrial spread was not documented in any patients who did not have lymphvascular space invasion within the cervix. Given that only one patient had parametrial micrometastasis, however, it is difficult to interpret the prognostic significance of this finding.

The necessity of parametrectomy for women with small, early-stage cervical cancer remains a subject of active debate. Previous reports have documented parametrial disease in 4-39%
of patients (2, 3, 6, 8, 9, 12, 16, 25, 32-35). Despite the frequency of parametrial tumor spread, several series have suggested that women with small volume tumors and other favorable pathologic characteristics are at a relatively low risk for parametrial metastasis (6, 16, 33). In a series of over 800 women with stage I cervical cancer who underwent radical hysterectomy, those with tumors less than 2 cm in diameter, with negative pelvic lymph nodes and superficial stromal invasion had a rate of parametrial involvement of less than 1% (6).

The goal of our study was to determine the rate of occult parametrial micrometastasis in women with early-stage cervical cancer. We sought to identify a group of patients at extremely low risk for parametrial spread who may be candidates for parametrium-sparing surgery. Our group previously demonstrated that women with tumors <2 cm in diameter without lymphvascular space invasion and negative pelvic nodes are at extremely low risk for parametrial metastasis. In our retrospective report, parametrial involvement was noted in only 0.4% of women whose tumors met the above pathologic criteria (33). In our current series, none of the patients who fell into this group had parametrial micrometastasis.

While it is encouraging that the rate of parametrial micrometastasis in our study was low, it is also a limitation in so much as the study is underpowered to determine the prognostic significance of parametral micrometastasis, as well as factors associated with micrometastatic disease. To identify the true rate of parametrial micrometastasis we examined multiple parametral sections from each patient. However, the entire parametrium was not examined, and as such we cannot exclude the possibility that additional parametrial micrometastases were not detected.

Our findings are reassuring in that it appears that occult parametral micrometastases are rare in women with stage IA and IB cervical cancer. As such, the routine performance of immunohistochemistry to identify parametral metastases is probably of little clinical utility. Our data provide further support to the concept that a low-risk subset of patients with early-stage cervical cancer exists and that these women may be candidates for less radical, parametrium-sparing surgical techniques. Conization or simple hysterectomy in combination with pelvic lymphadenectomy may be adequate treatment for these patients. As more conservative surgical approaches gain acceptance for other solid tumors, it is time to re-evaluate the necessity of radical en bloc resection of early cervical carcinomas.

References


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