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Management of uterine adenosarcomas with and without sarcomatous overgrowth

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HIGHLIGHTS

- Uterine adenosarcoma without sarcomatous overgrowth demonstrates a relatively indolent disease course that can be managed with surgery alone.
- No optimal chemotherapy regimen is identified for uterine adenosarcoma with sarcomatous overgrowth.

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ABSTRACT

Objectives. Uterine adenosarcomas (AS) are rare tumors composed of malignant stromal and benign epithelial components. We sought to evaluate the role of primary surgery, adjuvant treatments, and salvage therapies for patients with uterine adenosarcomas.

Methods. We identified all patients diagnosed with AS from 1990 to 2009 at our institution. Patient demographics, surgical procedures, sites of metastatic disease, and histologic features (e.g., presence of sarcomatous overgrowth, and heterologous elements) were collected. Treatment regimens and survival outcomes were evaluated.

Results. Thirty-one patients were evaluable for this study: 19 (61%) received up-front treatment at our institution and 12 (39%) received treatment for recurrent disease. Most of the up-front treated patients (15, 79%) were diagnosed with stage I disease and underwent hysterectomy (100%) with bilateral salpingo-oophorectomy (84%). Of the 19 patients treated at our institution from time of initial diagnosis, 5 (26%) patients recurred (median follow-up, 72.9 months; range, 3–154). In 5 patients with sarcomatous overgrowth (AS + SO), the 2-year progression-free and overall survival rates were both 20% versus 100% for 14 patients without sarcomatous overgrowth. Responses to systemic treatment of measurable disease were observed in patients with and without sarcomatous overgrowth, but no optimal treatment strategy could be identified for either groups.

Conclusions. Unlike AS without sarcomatous overgrowth, AS + SO is an aggressive disease with a high recurrence rate. In our series, no optimal adjuvant or systemic treatment strategy was identifiable but standard sarcoma chemotherapy regimens appear to have efficacy in both AS and AS + SO.

Introduction

Mullerian adenosarcomas are rare mixed mesenchymal and epithelial neoplasms usually arising from the uterus. These tumors consist of a benign-appearing epithelial component and a low-grade sarcomatous component frequently resembling endometrial stromal sarcoma [1]. The presence of sarcomatous overgrowth (AS + SO) appears to be most strongly associated with metastatic potential [2–7]. Other possible pathologic risk factors for metastatic disease include the presence of heterologous elements, depth of myometrial invasion, and tumor grade.

Management of these rare tumors has largely been inferred from the treatment of other uterine sarcomas. As such, surgical resection is viewed as the primary treatment modality [2,5,8]. Adjuvant therapy such as radiation has been recommended for early-stage, high-risk disease, although it remains unclear whether such adjuvant therapy has an impact on local control or overall survival [5,9]. In metastatic and recurrent settings, the use of systemic therapy is less understood. Chemotherapy is not generally recommended for treatment of adenosarcoma without sarcomatous overgrowth (AS). AS + SO may be treated with chemotherapy, but there are few data regarding its efficacy [10,11]. In addition, although a large proportion of these tumors are thought to be estrogen/progesterone (ER/PR) positive, response rates for hormonal therapies have not been widely reported [12–14].

We sought to evaluate the impact of surgery and current adjuvant and systemic therapies for uterine adenosarcomas in a comparatively

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large series of patients. Specifically, we sought to assess the role of radiation in the adjuvant setting and determine the efficacy of systemic chemotherapy and hormonal therapy in advanced or recurrent disease in patients with both AS and AS + SO.

Methods

Following the IRB approval, we performed a retrospective analysis of all patients diagnosed with uterine adenosarcoma from January 1, 1990 to December 31, 2009 who received treatment at the Memorial Sloan-Kettering Cancer Center (MSKCC). Patients were identified from a prospectively maintained institutional database. Uterine adenosarcoma was diagnosed according to standard criteria [1]. More specifically, tumors were characterized by a mixture of benign-appearing epithelial components and low-grade sarcomatous components. Sarcomatous overgrowth was diagnosed when ≥25% of the tumor volume consisted of the sarcomatous component. For patients that presented at the time of recurrence, slides from the initial hysterectomy specimen were reviewed to confirm the diagnosis of adenosarcoma in all cases. We excluded patients only presenting for consultation and patients lost to follow-up prior to completion of primary adjuvant therapy. Electronic medical records were reviewed for age at diagnosis, sites of metastatic disease, surgical procedures performed, tumor grade, and pathologic risk factors including deep myometrial invasion, sarcomatous overgrowth, and heterologous elements. Surgical stage was determined from operative and pathologic records at the time of diagnosis. Surgical stage based on the International Federation of Gynecology and Obstetrics (FIGO) 1988 criteria was compared to the recent FIGO 2009 staging criteria modifications [15]. All stage assignments were otherwise based on the FIGO 2009 staging criteria.

Response to treatment for patients with measurable disease on imaging was determined by evaluating subsequent imaging studies for disease response. If radiographic images were not available, interpretation of radiology reports and clinic notes were used to determine response. Evidence of increased size of tumor masses (≥20%) or new lesions was considered progression of disease. Substantial decreases of tumor masses (≥30%) were considered a partial response. Minimal changes in tumor size were considered to be stable disease. Progression-free and overall survival was determined for all patients. Primary progression-free survival (PFS) was defined as the interval from the date of primary surgery to the date of disease progression or last follow-up. Overall survival (OS) was defined as the interval from the date of primary surgery to the date of death or last follow-up. Time to progression for patients being treated for measurable disease was defined as the interval from initiation of therapy to date of disease progression as determined by imaging studies, physical examination or death, whichever event occurred first.

SPSS Statistics Version 19 was used for all analyses. Patient characteristics were compared using the Fisher exact test for discrete variables and the Mann–Whitney *U* test for continuous variables. Primary PFS and OS were determined for all patients who underwent primary surgery at MSKCC. We evaluated the relationship between survival and FIGO stage using univariate logistic regression.

Results

Patient characteristics and primary therapy

From January 1, 1990 to December 31, 2009, 41 patients were diagnosed with uterine adenosarcoma at our institution. Ten patients were excluded: 6 were seen only in consultation, 2 were lost to follow-up after surgery, and 2 had not yet completed primary therapy at the time of analysis. Of the remaining 31 evaluable patients, 19 were treated from initial diagnosis and 12 were seen for recurrent disease. The stage distribution based on the FIGO 2009 guidelines was as follows: 24 stage I (77%), 5 stage II (16%), and 2 stage III (6%). Five patients had their stage re-assigned based on recent changes to the FIGO staging system: 4 were downstaged and one was upstaged. Two patients were downstaged from IVB tumor to IIIA tumor due to changes in how intra-abdominal metastases are classified, while two others were downstaged from IIIA to IIA or IIB tumor due to changes in how adnexal or pelvic metastases are classified. One patient was upstaged from IIA to IIB due to changes in how mucosal cervical extension is classified.

Of the 19 patients treated at MSKCC from diagnosis, 5 demonstrated sarcomatous overgrowth (AS + SO) and 14 demonstrated adenosarcoma without sarcomatous overgrowth (AS). All patients underwent surgical resection consisting of laparoscopic-assisted vaginal hysterectomy (3 patients, 16%) or total abdominal hysterectomy (16 patients, 84%). Bilateral salpingo-oophorectomy (BSO) was performed in 16 patients (84%). Ovarian metastases were not identified in any patients undergoing BSO. Two premenopausal women with stage IA AS did not undergo BSO. Both patients are disease free more than 12 years since surgery. Pelvic lymphadenectomy and para-aortic lymphadenectomy were performed in 58% and 26% of patients, respectively. Four of 5 patients with AS + SO underwent at least pelvic lymphadenectomy. Lymph node metastases were not identified in any of the 11 patients who underwent lymphadenectomy (9 stage I, 2 stage II). Extrapelvic disease was identified in one patient with AS + SO (omentum) and none of the patients with AS. Three (60%) of the 5 AS + SO tumors also contained heterologous elements, while none of the AS tumors contained heterologous elements. Additional demographic and histologic data can be found in Table 1.

Adjuvant therapies

Adjuvant radiation was administered to 3 patients (16%). One of 5 patients with AS + SO (stage IIB) received adjuvant pelvic radiation and developed a recurrence in the upper abdominal lymph nodes and the abdominal wall outside of radiation fields 6 months after completing therapy. Two patients with AS received adjuvant radiation (pelvic or intra-vaginal) and their tumors did not recur during the study follow-up period (at least 54 months). None of these patients received adjuvant chemotherapy.

Predictors of recurrence and survival

Of the 19 patients treated at our institution from the time of diagnosis, 5 patients recurrent (26%), with a median follow-up of 72.9 months (range, 3.1–154.3 months; Table 2). The 5-year PFS and OS rates were 77% and 82%, respectively. Stage-specific 5-year PFS rates were as follows: stage I, 86%; stage II, 50%; and stage III, 0%. Stage-specific 5-year OS rates were as follows: stage I, 84%; stage II, 50%; and stage III, 0%. Four (80%) of 5 patients with AS + SO developed recurrent disease

Table 1
Characteristics of patients with uterine adenosarcoma treated from the time of diagnosis (n = 19).

Variable	AS N = 14 (%)	AS + SO N = 5 (%)
Age at diagnosis, median [range]	57 [27–76]	53 [44–72]
FIGO 2009 stage		
IA	9 (64)	2 (40)
IB	3 (21)	1 (20)
IIB	2 (14)	1 (20)
IIIA	0	1 (20)
Heterologous elements	0	3 (60)
Myometrial invasion	3 (21)	2 (40)
Pelvic lymphadenectomy performed	7 (50)	4 (80)
Positive pelvic lymph nodes	0/7	0/4
Para-aortic lymphadenectomy performed	3 (21)	2 (40)
Positive para-aortic lymph nodes	0/3	0/2
Extrauterine disease identified at the time of surgery	0	1 (20)
Residual disease after surgery	0	1/1

FIGO: International Federation of Gynecology and Obstetrics; AS: adenosarcoma without sarcomatous overgrowth; AS + SO: adenosarcoma with sarcomatous overgrowth.