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SARCOMAS (SR PATEL, SECTION EDITOR)

Uterine Adenosarcoma: a Review

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Abstract Adenosarcomas are rare malignancies of the female genital tract, accounting for approximately 5 % of uterine sarcomas. Occasionally, adenosarcoma occurs in the ovaries or in extra-uterine tissue, which may be related to endometriosis. These tumors are characterized by benign epithelial elements and a malignant mesenchymal component. Pathologic diagnosis is dependent on the identification of the characteristic morphologic features. The most common immunohistochemical markers for adenosarcoma are CD10 and WT1, but these are not specific. The most frequent presenting symptom is abnormal uterine bleeding. The majority of patients present with stage I disease, with a 5-year overall survival of 60 to 80 %. Survival is influenced by the presence of myometrial invasion, sarcomatous overgrowth, lymphovascular invasion, necrosis, and the presence of heterologous elements including rhabdomyoblastic differentiation. Patients with sarcomatous overgrowth have significantly increased risk of recurrence 23 versus 77 % and decreased 5-year overall survival 50 to 60 %. Standard of care treatment is total hysterectomy with bilateral salpingo-oophorectomy without lymphadenectomy, as the incidence of lymph node metastasis is rare. Retrospective data does not support the use of adjuvant pelvic radiotherapy in uterine adenosarcomas as no survival benefit is seen. Insufficient data exists to recommend routinely neoadjuvant or adjuvant chemotherapy for uterine adenosarcomas. Limited evidence exists for the role of hormonal therapy in uterine adenosarcomas. The PIK3/AKT/PTEN pathway is mutated in ~70 % of adenosarcomas, and this may represent a possible therapeutic target. This article reviews the current state of knowledge concerning uterine adenosarcoma and discusses the management of this rare tumor.

Keywords Sarcoma · Uterine · Adenosarcoma · Review · Ovarian · Soft tissue sarcoma

This article is part of the Topical Collection on *Sarcomas*

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Introduction

Uterine sarcomas represent approximately 1 % of female genital tract malignancies and 3 to 9 % of uterine cancers [1–4]. There are several different subtypes of uterine sarcomas including leiomyosarcoma representing 26 to 40 % of cases, endometrial stromal tumors 10 to 17 %, undifferentiated uterine sarcomas 3 to 5 %, and uterine adenosarcomas 5.5 to 9 % [2–7]. Formerly in this category, uterine carcinosarcomas have been re-classified as a dedifferentiated form of endometrial carcinoma [2]. Uterine adenosarcoma is arguably the rarest form of uterine sarcomas representing only ~0.2 % of all uterine malignancies. It has an age-adjusted incidence of 2 per 1,000,000 for Caucasians, 3 per 1,000,000 for African Americans, and 1 per 1,000,000 for other ethnic groups in the US population [3].

In 1974, Philip B. Clement and Robert E. Scully provided the initial description of uterine adenosarcoma. They described it as an "admixture of benign appearing neoplastic glands and a sarcomatous stroma, creating a striking resemblance to the cystosarcoma phyllodes of the breast" [8]. These tumors are composed of a benign epithelial component and a malignant mesenchymal component, which differentiates them from carcinosarcomas, which have a malignant epithelial component [5, 9]. Previous reviews only briefly discuss uterine adenosarcomas, given the rarity of this subtype. Additionally, minimal data exists to guide treatment decisions in this rare uterine sarcoma. This review will focus specifically on adenosarcomas discussing the clinical and pathologic characteristics, prognosis factors, and recommendations for treatment.

Clinical Features

Uterine adenosarcoma was initially described as a tumor of the elderly population with a peak incidence in the seventh to ninth decades [7, 8, 10]. Subsequent small series showed the median age at diagnosis for uterine adenosarcomas varied from 41 to 65.7 years [4, 5, 9, 11–16]. The five largest single institution series of 100, 74, 64, 55, and 41 patients showed median ages of 58, 55, 61, 50, and 54 years with ages ranging from 13 to 94 years [5, 17••, 18–20]. The largest series from the SEERs database, of 544 adenosarcoma patients showed that 51.5 % of patients were between the age of 40 and 65 years, 38.4 % of patients were older and 65 years, and there are less than 10 % of patients younger than 40 years [21]. There is no statistically significant difference in the incidence of adenosarcoma by ethnicity [3, 21]. The majority of uterine adenosarcomas arise from the uterus. However, adenosarcoma can arise from other gynecologic tissue. The second most common site for adenosarcoma is the ovaries [19, 20, 22–46], with the largest series of ovarian adenosarcoma reported involving 40 patients [47]. The majority of these tumors are unilateral in 97.5 %, but there was one patient that presented with adenosarcoma in both ovaries [47]. Adenosarcoma can also arise from the cervix [11, 19, 20, 48–75], vagina [76–80], fallopian tubes [19, 31, 81], or even from primary pelvic or peritoneal sites, including the omentum, particularly in those with a history of endometriosis [14, 82–97]. There are multiple case reports of adenosarcoma arising from the kidneys or retroperitoneum [98–103], a case report of a bladder adenosarcoma, also arising from endometriosis [104], three case reports of adenosarcoma arising from the liver in patients with cirrhosis or hepatic endometriosis [105–107], and another two case reports of adenosarcoma arising in an abdominal scar in a patient with a history of endometriosis [108] or from inguinal endometriosis [109]. Thus, while most arise from the uterus or other gynecologic tissue, rare extra-uterine/pelvic adenosarcomas do occur.

Risk Factors

Many of these extra-uterine adenosarcoma cases, at least, those within the abdomen or pelvis, reportedly arise in the setting of endometriosis or in patients with a history of endometriosis [110]. A definitive causal link has not yet been established between adenosarcoma and endometriosis. However, in a series of 1000 patients with biopsy-proven endometriosis, the incidence of cancer was 5.5 %, with the majority of tumors being endometrioid carcinoma followed by clear cell carcinoma and adenosarcoma [111]. All adenosarcoma cases were pathologically documented to arise from within endometriosis [111], as noted in previously described case reports. This study required the presence of endometrial-type epithelium and endometrial-type stroma to make the diagnosis of endometriosis. Thus, ectopic uterine tissue may undergo malignant transformation, some of which results in the development of adenosarcoma. Whether the epithelioid or mesenchymal component leads to the development of adenosarcoma is uncertain. Furthermore, the cell of origin of uterine adenosarcomas has yet to be determined. While many cases of extra-uterine adenosarcoma can be linked to endometriosis, carcinomas are 20 times more likely to arise from endometriosis [111]. The underlying molecular mechanisms leading to this malignant transformation into different cancer types is poorly understood. A common pathway may be DNA damage resulting from repeated oxidative stress caused by retrograde menstruation and iron overload [112]. While endometriosis may be a risk factor for the development of adenosarcoma, it is likely not the sole risk factor.

An additional risk factor for the development of uterine adenosarcomas is treatment with tamoxifen or other estrogen-modulating agents. Tamoxifen is a selective estrogen receptor modulator (SERM) that has a partial estrogen agonist effect on the endometrium. There are multiple case reports of uterine adenosarcoma developing in patients on treatment with tamoxifen or other selective estrogen receptor modulators for the treatment of breast cancer [113–122]. However, of the multiple changes that can occur with estrogen or tamoxifen therapy, adenosarcoma is rarely observed [123]. In a large cohort of patients treated with tamoxifen to prevent breast cancer, the relative risk of developing uterine cancer was 2.5, most of which were uterine carcinomas [124]. Thus, similarly to endometriosis, treatment with tamoxifen increases the risk for neoplasms of uterine origin, which can rarely include uterine adenosarcoma. Additional potential risk factors for adenosarcoma include previous pelvic irradiation [5], prolonged estrogen exposure [125], or exposure to other SERMs, such as toremifene [122].

Presenting Symptoms

Uterine adenosarcoma typically presents as a polypoid mass within the uterine cavity. This mass bleeds easily. Consequently, most patients present with abnormal uterine bleeding, 65 to 76 % in three of the larger series [5, 17••, 20]. As a result, the majority of patients are diagnosed with stage I disease (FIGO staging), 73.4 to 82 % in the largest series [3, 7, 12, 17••, 18, 21]. The next most common presenting symptom/sign is pelvic pain or demonstration of a pelvic mass, noted in 12 to 33.3 % [7, 11, 17••, 20]. The most frequent presenting symptoms for ovarian adenosarcoma is abdominal discomfort and distension [47]. Additionally, patients may present with an abnormal vaginal discharge, 11.1 % in one study [11]. On examination, patients may have an enlarged uterus, or cervical, or endocervical polyps [5, 6, 17••, 20]. Rarely, abnormalities found on a pap smear leading to the diagnosis of a uterine adenosarcoma [126, 127]. Finally, some patients undergoing a hysterectomy for uterine fibroids are incidentally found to have uterine adenosarcoma.

Pre-operative Imaging

Before surgical resection, most patients will have imaging of the abdomen and pelvis with ultrasound, CT scan or MRI to examine the local extent of disease with MRI being the preferred modality [128]. Additionally, patients should have a CT scan of the lung to rule out lung metastasis. Imaging findings are generally not specific to establish an adenosarcoma diagnosis. Features suggestive of uterine adenosarcoma are a regular well-demarcated mass that is hypointense and heterogeneous on T1, multi-septated cystic appearance on T2, and low signal on DWI [129–131]. However, MRI characteristics of uterine sarcomas can overlap [129].

Pathologic Characteristics

Macroscopic Characteristics

Uterine adenosarcomas usually present as a soft polypoid lobulated mass with clefts or cysts within the uterine cavity. Cases of multiple polyps have been reported. These tumors commonly arise from the endometrium, which can occasionally include the lower uterine segment, though these tumors have been noted to arise from the endocervix or myometrium as well. The margins of these tumors are well-defined. In the largest series, the size of these tumors ranged from 1 to 17 cm in maximum dimension, with a mean size of 5 cm [5, 132]. The tumor can fill the entire uterine cavity and may project through the cervical os. Focal hemorrhage and necrosis can be grossly identified. Ovarian adenosarcoma are on average larger than uterine adenosarcoma. The size of ovarian adenosarcoma tumors ranged from 5.5 to 50 cm, with a mean of 14 cm [47].

Microscopic Characteristics

Uterine adenosarcomas are composed of a benign appearing glandular epithelial component, and a malignant mesenchymal component [5, 133]. This biphasic cellular differentiation is characteristic of adenosarcomas [134]. This histologic appearance was initially described as reminiscent of a phyllodes tumor of the breast [132]. The epithelial glands are rounded or more commonly slit-like. The epithelial morphology is usually endometrioid, though mucinous, serous, and squamous epithelium have been noted as well [5, 132]. Occasionally, the epithelial component can have cellular atypia. The stromal or mesenchymal component is characterized by spindled and/or round cells that concentrate around the glandular elements forming peri-glandular cuffs [2]. The stromal cells in these peri-glandular cuffs exhibit varying degrees of cellular atypia and increased mitotic activity [132]. In one study, the mean mitotic rate was 9 mitotic figures per 10 HPF [5]. A mitotic rate 1 to 2 mitotic figure per 10 HPF is required by the WHO criteria to make the diagnosis of adenosarcoma [2]. However, it has been argued that the diagnosis of adenosarcoma can be made in the absence of mitotic figures if the characteristic architecture is present with peri-glandular cuffing [132, 134, 135]. In most adenosarcomas, the mesenchymal component is low grade, resembling endometrial stromal sarcomas [134]. However, up to 10 to 25 % of adenosarcomas have heterologous elements including rhabdomyoblasts, sex cord-like stromal elements, chondrosarcoma elements, liposarcoma elements, or smooth muscle-derived elements [2, 5, 132]. Adenosarcomas with greater than 25 % of the tumor composed of pure high-grade sarcoma without a glandular component are designated as adenosarcoma with sarcomatous overgrowth, found in 8 to 54 % of cases [2, 5, 9, 10, 17••, 19]. High-power field examination of these areas shows large and anaplastic stromal cells resembling high-grade undifferentiated sarcoma. Myometrial invasion, lymphovascular invasion, and necrosis can be seen. Myometrial invasion is found in 16 % to 74 % of cases [5, 7, 9, 17••, 19, 20]. Lymphovascular invasion is found in 9 to 16 % of cases [4, 7, 9, 17••]. Necrosis was found in 35 % of cases in two studies [4, 9].

Immunohistochemistry

There are no immunohistochemical markers that are pathognomonic for adenosarcoma, with the diagnosis of these tumors largely dependent on the morphologic features. The most common immunohistochemical markers are CD10 (71

to 100 %) and WT1 (79 %), a similar immunophenotype to endometrial stromal tumors [136–140]. In a study of 35 patients, there was a loss of CD10 expression in patients with sarcomatous overgrowth (28 %), compared to those without sarcomatous overgrowth (82 %) [136]. This result was confirmed in a second study [137]. Additional markers that can be present in adenosarcomas are vimentin (86 %), smooth muscle actin (50 to 68 %), desmin (32 to 62.5 %), CD34 (35 %), calretinin (12 %), and AE1/3 cytokeratin (25 to 27 %) [136, 138–140]. Inhibin and c-kit are rarely weak and focally positive [136, 141, 142]. The Ki67-labeling index is usually <5 % in adenosarcoma but increases to ~20 % in areas of periglandular cuffing, and in those patients with sarcomatous overgrowth [136, 139]. The epithelial component of adenosarcomas typically stains for cytokeratins, EMA, estrogen receptor (ER), progesterone receptor (PR), and rarely CD10 [136, 141]. PDGFR-α was overexpressed by immunohistochemistry in the stromal component of most adenosarcoma patients [19]. Nuclear β-catenin expression was observed in 68 % of uterine adenosarcomas [143].

Uterine adenosarcomas stain for the estrogen receptor (33 to 75 %), progesterone receptor (50 % to 76 %) and androgen receptor (AR) (35 %) [136, 137, 144]. One report showed uterine adenosarcomas had greater PR expression compared to ER expression [136]. However, the extent of immunohistochemical staining for ER and PR varies by a wide margin 15 to 95 % [136]. Furthermore, loss of ER and PR expression has been associated with sarcomatous overgrowth [136]. In one study, staining for ER was 78 % and PR 81 % in patients without sarcomatous overgrowth, while staining for ER was 14 % and PR 57 % in patients with sarcomatous overgrowth [136]. Whether ER and PR are indeed prognostic factors in uterine adenosarcoma has yet to be determined. The variability in expression, the variability in the intensity of staining, and loss of expression in those patients with sarcomatous overgrowth limits the utility of survival analyzes in small sample sizes. The utility of ER and PR as predictive markers for response to hormonal therapy in uterine adenosarcomas has not been studied.

Molecular Classification

Molecular classification of tumors, in addition to helping in pathologic diagnosis, can help identify potential therapeutic targets. There has been only one targeted genomic analysis of uterine adenosarcoma patients [145••]. This analysis included twelve cases of adenosarcoma without sarcomatous overgrowth and six cases of adenosarcoma with sarcomatous overgrowth. Targeted genomic analysis revealed a mean copy number variation (CNV) of 24.6 in patients with sarcomatous overgrowth versus 5 in patients without sarcomatous overgrowth, with more CNV gains in patients without sarcomatous overgrowth and more CNV losses in patients with sarcomatous overgrowth. This finding indicates a genetic difference in adenosarcoma patients with sarcomatous overgrowth compared to those without sarcomatous overgrowth. There was no difference in the frequency of single nucleotide variations detected. The most common chromosome altered in adenosarcoma was chromosome 8 [146••]. The most frequent copy number gains included *MYBL1* located at 8q13.1 identified in four patients.

The most common mutations identified were *PTEN* mutations in three patients, *AKT* mutations in three patients, and *PIK3* mutations in seven patients. Mutations in the *PTEN*/*AKT*/*PIK3* pathway represented 72 % of patients and, therefore, is the most frequent pathway altered in uterine adenosarcomas, suggesting a possible therapeutic target. This molecular pathway is currently targetable by mTOR inhibitors, though the efficacy of mTOR inhibitors has not been tested in uterine adenosarcomas. Additionally, *MDM2* and *CDK4* gain were present in five patients. MDM2 overexpression by immunohistochemistry was shown in two cases of adenosarcoma [10] suggesting a possible role of MDM2 or CDK4 inhibitors in select patients with adenosarcoma. Loss of tumor suppressor genes *CDKN21* was shown in five patients, *BAP* 1 in three patients, and *RB1* in three patients.

There were two *TP53* mutations detected in patients with sarcomatous overgrowth, a missense mutation with an associated p53 overexpression by immunohistochemistry and a frame-shift mutation leading to a null immunophenotype. Mutated p53 proteins can be more resistant to degradation, resulting intracellular accumulation and overexpression on immunohistochemistry. Staining by immunohistochemistry for p53 in four small studies showed overexpression in 2/11, 5/32, 0/6, 9/11 of patients [10, 19, 147, 148]. There was a suggestion of increased p53 expression in those patients with sarcomatous overgrowth versus those without sarcomatous overgrowth again suggesting a genetic difference between adenosarcoma with sarcomatous overgrowth versus without sarcomatous overgrowth that may account for the difference in clinical behavior. [10]. Unfortunately, while p53 may be frequently mutated in adenosarcomas with sarcomatous overgrowth, similar to sarcomas in general, this pathway is not currently targetable.

Other pathways examined in adenosarcomas, but are rarely mutated or overexpressed, so likely do not play a central role in the pathogenesis of adenosarcomas, include *EGFR*, *HER-2-Neu*, and the mismatch repair pathway [19, 147, 149, 150]. Interpretation of these limited genomic and immunohistochemistry results is difficult due to small sample sizes. Also, the expression on IHC does not necessarily correlate with mutational status nor does it necessarily correlate with the critical dependence of the tumor on these molecular pathways. Further studies are required to elucidate the role of p53, MDM-2, CKD4, and the *PTEN*/*AKT*/*PIK3* pathway in the development of uterine adenosarcoma

and whether these pathways represent a potential therapeutic target in these tumors.

Prognosis and Prognostic Factors

Patterns of Recurrence

Small series (8 to 31 patients) of uterine adenosarcoma patients have noted recurrences varying from 14.3 to 45 %, with larger series (>40 patients) showing recurrence in 23 to 46 % of patients [5, 7, 9, 10, 12, 17••, 18–20, 151]. Table 1 shows the incidence of recurrent adenosarcoma in all patients and by the presence of sarcomatous overgrowth as well as the location of recurrences. Part of this variation can be explained by small samples sizes in studies. The other part is due to differences in the median follow-up time (range 2 to 7.5 years), as the median time to recurrence in adenosarcoma can vary from 1 to 5 years, with recurrences occurring as early as 2 months and as late as 11.6 years [5, 17••, 18, 20, 151]. Overall, approximately one third to one half of adenosarcoma patients will develop recurrences over a period of ~10 years. Sarcomatous overgrowth does influence the chances of recurrence. Small series of 6 to 27 patients with adenosarcoma without sarcomatous overgrowth showed recurrences in 7.1, 14.3, 26, and 50 % of patients [9, 10, 12, 20]. Whereas, in a series of 11 to 74 patients with adenosarcoma with sarcomatous overgrowth, recurrences were seen in 40, 43.7, 67, 70, 77.4, 80, and 81.8 % of patients [9, 10, 12, 13, 15, 17••, 20]. For ovarian adenosarcomas, the majority of recurrences were local, and the relapse-free survival was 23 % [47].

Overall Survival

The largest retrospective series of 100 by Clement et al. reported a 60.2 % overall survival with a median follow-up of 5.9 years [5]. A more recent report showed a similar median overall survival of 48 months in a series of 41 patients [20]. An epidemiology study from Norway in 419 patients reported a 5-year overall survival of 76 % and a 10-year overall survival of 61 % for patients with stage I uterine adenosarcoma [4]. Smaller series have noted a 5-year overall survival ranging from 69 to 87 % [7, 10, 12]. For ovarian adenosarcomas, the 5-year overall survival 64 %, and 10-year overall survival 46 % [47]. These outcomes are worse than for uterine adenosarcoma.

Sarcomatous Overgrowth

Survival is influenced by the presence of sarcomatous overgrowth, with several small series showing a significant difference in overall survival corresponding to sarcomatous overgrowth status [19, 20]. A median overall survival of only 13 months was reported in one series of uterine adenosarcoma patients with sarcomatous overgrowth [13]. In a series of 31 patients, a 2-year overall survival and progression-free survival was 20 % in patients with sarcomatous overgrowth, and 100 % in patients without sarcomatous overgrowth [12]. Patients without sarcomatous overgrowth have a 5-year overall survival ranging from 69.3 to 80 % [10, 18]. Patients with sarcomatous overgrowth have a 5-year overall survival ranging from 50 to 60.7 % [10, 18]. A large series of 74 patients showed the median overall survival of 55.4 months in patients with sarcomatous overgrowth and 112.4 months in patients without sarcomatous overgrowth, hazard ratio (HR) on multivariate analysis 2.45, 95 % CI 1.26–4.76, $p = 0.008$ [17••]. Median progression-free survival differed as well with 29.4 versus 105.9 months for adenosarcoma with sarcomatous overgrowth and adenosarcoma without sarcomatous overgrowth, respectively. The HR on multivariate analysis was 2.58, 95 % CI 1.37–4.84, $p = 0.003$ [17••]. Similar to uterine adenosarcoma, sarcomatous overgrowth was present in 30 % of ovarian adenosarcomas [47].

Staging/Myometrial Invasion

The current staging system for uterine adenosarcoma is based on the presence and extent of myometrial invasion as well as extent of disease outside the uterus. Patients with stage Ia have no myometrial invasion, patients with stage Ib have invasion into the myometrium that is less or equal to ½ of the myometrial thickness, and patients with stage Ic have invasion into the greater than ½ of the myometrium. The most recent 2009 FIGO staging for uterine adenosarcomas is listed in Table 2 [152]. The majority of patients are diagnosed with stage I disease 73.4 to 82 % [3, 7, 10, 12, 17••, 18, 21]. Distribution among stage one varies with stage Ia 35.3 to 42.2 %, Stage Ib 21.0 to 28.1, and stage Ic 3.9 to 3.1 % [18, 21]. Patients present with stage II in 6 to 16 % of cases, stage III in 4 to 7 % of cases, and stage IV in 3 to 5 % of cases [3, 12, 17••, 21].

The 5-year overall survival varies between stages, with stage I patients having a 63 to 86 % to 5-year overall survival, stage II patients having a 50 to 69 % 5-year overall survival, stage III patients having a 0 to 48 % 5-year overall survival, and stage IV patients having a 15 % 5-year overall survival [12, 21]. Survival, also, varies with the presence and extent of myometrial invasion with stage Ia (no myometrial invasion) patients having a 83.3 to 84 % 5-year overall survival, stage Ib (invasion ≤½ myometrial thickness) patients having a 63 to 69 % 5-year overall survival, and stage Ic (invasion >½ myometrial thickness) patients have a 63 % 5-year overall survival [18, 21]. The extent of extra-uterine spread is associated with worse clinical outcomes with decreased progression-free survival and disease-free survival on

Table 1 Patterns of recurrence in adenosarcoma

	No. of patients	Median time to recurrence	Median follow-up time	Recurrences in all patients *n* (%)	Recurrences in patients with SO *n* (%)	Recurrences in patients without SO *n* (%)	Local recurrences *n* (%)	Distant recurrences *n* (%)
Krivak et al. [13] (all pts had SO)	11	NR	NR	9/11 (81.8 %)	9/11 (81.8 %)	–	6/11 (54 %)	5/11 (45 %)
Kaku et al. [9]	31 (30)	NR	38.3 months	9/30 (30 %)	7/16 (43.7 %)	2/14 (14.3 %)	6/30 (20 %)	3/30 (10 %)
Gallardo et al. [19]	55 (29)	NR	92 months	6/29 (20.7 %)	NR	NR	NR	NR
Verschragen et al. [20]	41 (37)	12 months	NR	14/37 (38 %)	6/9 (67 %)	7/27 (26 %)	13/36 (36.1 %)	3/36 (8.5 %)
Tanner et al. [12]	31 (19)	NR	72.9 months	5/19 (26 %)	4/5 (80 %)	1/14 (7.1 %)	NR	NR
Clement et al. [5, 8, 15]	100	40.8 months	NR	23/100 (23 %)	7/10 (70 %)	NR	22/100 (22 %)	2/100 (2 %)
Zaloudek et al. [151]	25	60 months	NR	10/25 (40 %)	NR	NR	NR	NR
Benito et al. [7]	8 (7)	NR	NR	1/7 (14.3 %)	NR	NR	NR	NR
Blom et al. [10]	11	NR	NR	5/11 (45 %)	2/5 (40 %)	3/6 (50 %)	2/11 (18 %)	3/11 (27 %)
Bernard et al. [18]	64 (45)	21.2 months	24 months	16/45 (35.6 %)	NR	NR	11/43 (25.6 %)	7/43 (16.3 %)
Carroll et al. [17••]	74	18.3 months	56.5 months	34/74 (46 %)	24/31 (77.4 %)	10/43 (23.3 %)	31/74 (42 %)	2/74 (3 %)

Not all patients in each series were evaluable for recurrence. The total number of patients in each series is listed in column one with patients evaluable for recurrence in parenthesis. One patient in the Verschragen series and two patients in the Bernard series did not have sites of recurrence disease listed

NR not reported, *SO* sarcomatous overgrowth, *mo* months

Table 2 2009 FIGO (International Federation of Gynecology and Obstetrics Staging for Uterine Adenosarcomas) [152]

Stage	Definition
I	Tumor limited to the uterus
Ia	Tumor limited to endometrium/endocervix with no myometrial invasion
Ib	Less than or equal to half myometrial invasion
Ic	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIa	Adnexal involvement
IIb	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen)
IIIa	One site
IIIb	>one site
IIIc	Metastasis to pelvic and/or para-aortic lymph nodes
IV	
IVa	Tumor invades bladder and/or rectum
IVb	Distant metastasis

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multi-variate analysis [17••]. Additionally, the presence and extent of myometrial invasion correlate with the risk of tumor recurrence [9, 18, 151], 13.5 versus 35.3 % in one series [5].

Other Prognostic Markers

The prognostic value of age and race in uterine adenosarcomas has been evaluated in a limited number of reports. An analysis of the SEERs database from 1988 to 2006 identified 544 patients with adenosarcoma [21]. This analysis suggested a difference in prognosis based on race and age. Black women with adenosarcoma were 16 % more likely to die from their disease than caucasian women, HR 1.16; 95 % CI 1.04 to 1.29 [21]. Older age was associated with worse prognosis in this study, and in a second smaller retrospective report, HR 1.02, 95 % CI 1.00 to 1.04, $p = 0.016$ [17••]. These results were based on univariate analysis but suggest age and race being potential prognostic markers for uterine adenosarcoma.

Other potential pathologic prognostic markers, in addition to sarcomatous overgrowth and myometrial invasion, are initial size of the tumor, lymphovascular invasion, tumor necrosis, cellular atypia, the number of mitosis, and presence of heterologous elements including rhabdomyoblasts. Tumor size varies from 0.1 cm to >20 cm in uterine adenosarcoma, with 65 % of patients having tumors 0.1 to 5 cm and 26 % of patients having tumors 6 to 10 cm [4], with a median tumor size varying from 6 to 20 cm [17••, 19]. Lymphovascular invasion is noted in 9 to 16 % of uterine adenosarcomas [4, 7, 9, 17••]. Necrosis has been noted in up to 35 to 58 % of uterine adenosarcoma patients [4, 9]. Mild cellular atypia was noted in 61 % of tumors, moderate atypia in 26 % of tumors, and severe atypia in 9 % of tumors [4]. Mitosis have been noted to be 0 to 5 per 10 HPF in 19 to 65 % of uterine adenosarcoma patients, 6 to 10 per 10 HPF in 17 to 19 % of patients, and >10 per 10 HPF in 17 to 61.2 % of patients [4, 5, 9]. Heterologous elements have been noted in 20 to 48 % of patients with uterine adenosarcoma [5, 9, 17••, 19]. The presence of lymphovascular invasion has been reported to be associated with increased risk of tumor recurrence, 24 versus 60 % in patients without lymphovascular invasion and patients with lymphovascular invasion, respectively [9]. Lymphovascular invasion is also associated with an inferior progression-free survival, disease-free survival, and overall survival, HR 3.5, 95 % CI 1.42–8.63, $p = 0.007$ [17••]. Necrosis and cellular atypia were associated with significantly worse survival on univariate analysis of 23 uterine adenosarcoma patients, $p = 0.006$ and $p = 0.02$, respectively [4]. Low mitotic count (<5 mitoses per 10 HPF) versus high mitotic count is associated with increased risk of tumor recurrence [9]. Additionally, patients with heterologous elements are at increased risk of recurrence and worse prognosis [9]. Furthermore, the presence of rhabdomyoblasts may confer a significantly worse prognosis. Correlation has been documented between with presence of lymphovascular invasion, presence of tumor necrosis, increased mitotic count, and presence of heterologous elements, with sarcomatous overgrowth in small studies [9, 10]. No large multivariate analysis has been reported examining all of these factors. However, available evidence does suggest an interconnected relationship between these factors and sarcomatous overgrowth. Overall, myometrial invasion and sarcomatous overgrowth can be considered two of the most significant prognostic markers in uterine adenosarcoma.

Treatment

Surgery

The standard treatment for uterine adenosarcoma is surgical resection with a total hysterectomy, performed by an experienced gynecologist oncologist [2, 132, 134]. Laparoscopic hysterectomy with morcellation is not recommended, as this leads to tumor seeding of the pelvic and abdominal cavity usually resulting in the development of sarcomatosis and poor clinical outcome [153, 154]. Occasionally, young patients desiring to preserve fertility with small, non-myometrial invasive, non-sarcomatous overgrowth tumors have been treated with polypectomy alone or polypectomy with chemotherapy [5, 17••, 155]. Though, this would not be the preferred approach, as these patients are still at risk for recurrent disease. Hysterectomy should be considered after childbearing is completed. Additionally, bilateral salpingo-oophorectomy (BSO) is also recommended as standard of care [156]. The incidence of the spread of the tumor to the adnexa was 17 %, and ovaries were 8 % in one series, where the majority (81 %) of patients underwent BSO [17••]. Other series have shown ovarian involvement in 0 to 2 % of patients [5, 12]. Though a difference in progression-free survival was not shown in this series, HR 1.69, 95 % CI 0.76–3.78, this analysis may have been limited by small patient numbers. The efficacy of ovarian preservation in uterine adenosarcomas is limited to case reports [155, 157, 158]. Given the risk of local spread to the adnexa and ovaries, and worse prognosis of patients with stage II compared to stage I disease reported in prior series, BSO should be considered with total hysterectomy. Resection of the ovaries will lead to a post-menopausal state, with a decrease in estrogen and progesterone levels. As noted above, many uterine adenosarcomas express estrogen or progesterone receptor. Whether BSO leading to reduced estrogen and progesterone level is beneficial in the long-term for these patients is undetermined, as the role of estrogen in the progression or recurrence of these patients is still uncertain. Unlike uterine carcinomas, lymphadenectomy is not recommended, as the incidence of metastasis to regional lymph nodes is very low 0 to 6.5 % [9, 12, 17••, 18, 21]. Additionally, no overall survival benefit, HR 0.83, 95 % CI 0.41–1.66, $p = 0.59$, or progression-free survival benefit, HR 0.67, 95 % CI 0.35–1.3, $p = 0.24$, has been shown with the addition of lymphadenectomy to hysterectomy [17••].

Adjuvant XRT

Adjuvant radiation therapy to the pelvis is commonly used in patients with uterine sarcomas, including uterine adenosarcomas to reduce the risk of local recurrence. In the largest series, between 17.5 and 24 % patients receive radiotherapy to the pelvis or vaginal cuff [17••, 21]. Treatment modalities include both external beam radiotherapy and brachytherapy. There are no randomized or prospective trials examining the use of radiation therapy in patients with uterine adenosarcoma. Instead, treatment guidelines draw parallels from the treatment of other uterine sarcomas or uterine carcinomas. The National Compressive Cancer Network (NCCN) uterine cancer guidelines recommend that adjuvant radiation be considered in patients with stage II to IVa high-grade endometrial stromal sarcomas and leiomyosarcoma [156]. This is a category 2A recommendation based on lower-level evidence, but uniform NCCN consensus that the intervention is appropriate. The recommendation is based in part on the American Society for Radiation Oncology endometrial carcinoma treatment guidelines [159] and may not apply to uterine sarcomas. In fact, a phase III study of adjuvant radiotherapy in uterine sarcomas showed no difference in overall survival or disease-free survival [160]. This study included patients with leiomyosarcoma, carcinosarcoma, and a few patients with endometrial stromal sarcomas. There were no patients with uterine adenosarcoma. There was a significant difference in loco-regional recurrence when carcinosarcoma and leiomyosarcomas patients were combined. However, the incidence of local recurrence in leiomyosarcoma patients alone was 20 % in the radiotherapy group versus 24 % in the observation group, a difference of only two patients [160]. Also, several retrospective reviews have shown no benefit regarding overall survival with adjuvant radiation therapy in uterine adenosarcoma patients [12, 17••, 21]. With limited data on the efficacy of adjuvant radiation therapy and known side effects of pelvic radiation [161], it is difficult to recommend this as an adjuvant treatment modality in uterine adenosarcomas.

Adjuvant Chemotherapy

Given the rarity of this disease, no adenosarcoma-specific prospective or randomized controlled trials evaluating the role of adjuvant or neoadjuvant chemotherapy exist. Additionally, most uterine sarcoma trials that evaluate the role of chemotherapy in the adjuvant or metastatic setting have not included adenosarcoma patients. Notably, no adenosarcoma patients were included in the initial gemcitabine/docetaxel uterine leiomyosarcoma studies [162–165]. The current GOG 0277 trial, which is evaluating the role of gemcitabine/docetaxel and doxorubicin in the adjuvant setting for uterine leiomyosarcomas, excludes adenosarcoma patients. A systematic review of chemotherapy in advanced uterine sarcomas showed responses in mixed mesodermal tumors to cisplatin, doxorubicin, cyclophosphamide, ifosfamide, paclitaxel, and dacarbazine,

though in these older studies, adenosarcoma was not differentiated from the more common carcinosarcoma [166].

Only case series or case reports document the use adjuvant chemotherapy in adenosarcoma patients, Table 3. The limited number of patients in these series, the short follow-up, the diversity of chemotherapy regimens, and the inconsistent reporting of sarcomatous overgrowth prevent any effective analysis of neoadjuvant or adjuvant chemotherapy on survival outcomes [17••, 18]. Consequently, data for the effectiveness, benefit, or harm of neoadjuvant or adjuvant chemotherapy in uterine adenosarcomas is lacking. In the absence of data, appropriate clinical judgment must be utilized. Adenosarcoma patients without sarcomatous overgrowth and without myometrial invasion have improved outcomes with surgery alone compared to those patients with sarcomatous overgrowth and/or myometrial invasion, as evidenced by differences in disease-free survival, overall survival, and recurrence rate. Thus, patients without sarcomatous overgrowth and/or without myometrial invasion are unlikely to derive any benefit from adjuvant chemotherapy. However, patients with sarcomatous overgrowth can have survival as limited as 13 months [13], with a 5-year overall survival of only 50 to 60 % compared to 70 to 80 % for patients without sarcomatous overgrowth. In high-risk uterine adenosarcoma patients with myometrial invasion or sarcomatous overgrowth, adjuvant chemotherapy may be considered on an individual basis, in an attempt to decrease the risk of recurrence and improve the chance of cure, after a discussion with patients about the risks of treatment. Patients must have adequate performance status, limited medical co-morbidities, and understand the limited data regarding adjuvant chemotherapy in uterine adenosarcomas.

Regarding the choice of an adjuvant chemotherapy regimen, again data is limited. Adenosarcomas are tumors composed of benign epithelial and malignant mesenchymal elements. It is reasonable to select chemotherapeutic agents with known efficacy against mesenchymal tumors, such as doxorubicin/ifosfamide, or gemcitabine/docetaxel. In the available reports from patients with recurrent or metastatic adenosarcoma, complete responses have been noted with doxorubicin-based regimens and gemcitabine/docetaxel, Table 4, indicating that these regimens are the most reasonable to consider in the adjuvant setting. In such a rare disease, where a prospective clinical trial in unlikely to occur, treatment decisions must be made in the absence of high-quality evidence.

Hormonal Therapy

Evidence for hormonal therapy in the adjuvant, recurrent, or metastatic setting is limited to case reports. Agents used include GnRH agonists (leuprolide), synthetic progesterones (megestrol acetate, medroxyprogesterone, dienogest), selective estrogen receptor modulators (tamoxifen, raloxifene), and aromatase inhibitors (anastrozole, letrozole). Responses have been noted for between 10 months to 7 years [17••, 176–179]. Responses have occasionally been correlated with the presence of ER and PR staining, with the loss of response correlated with reduced ER/PR in one case report [179]. However, this finding has yet to be evaluated in a systematic manner. Further investigations are required to identify the preferred hormonal agent, and define the subset of patients that may derive benefit from hormonal therapy. Certainly ER/PR positivity and intensity of staining are attractive biomarkers, but these have not yet been shown to be predictive of response to hormonal therapy.

Treatment for Recurrent or Metastatic Disease

The most common location for recurrent disease is locally within the pelvis or abdominal cavity. Sarcomatosis is a common complication. Local recurrences were seen in 18, 20, 25.6, 36.1, 50, and 54 % of patients in small series [8–10, 13, 18, 20]. Larger series of 74 to 100 patients showed local recurrence in 22 to 42 % of patients [5, 17••]. Distant metastasis is less common than local recurrence in adenosarcoma. Small series showed distant metastasis in only 5, 8.3, 10, and 16.3 % of cases, though series with mostly adenosarcoma with sarcomatous overgrowth showed distant metastasis in 27 to 45 % of patients [8–10, 13, 18, 20, 180]. Larger series show a rate of distant metastasis to be only 2 to 3 % [5, 17••]. The most common locations for distant metastasis are the lung or liver, though occurrences of metastatic disease to the bone, kidney, spleen, and even rarely the brain occur. Treatment options for locally recurrent or metastatic adenosarcoma include surgical resection of local recurrence or distant metastasis and systemic chemotherapy. Radiation is appropriate for palliation of metastatic lesions. Hormonal therapy can be considered as well. Benefit for secondary cytoreduction has been suggested in two series. Out of 34 recurrences, 62 % underwent a second surgery, with a median overall survival of 58.4 versus 30.1 months, HR 0.68, 95 % CI 0.28–1.67, $p = 0.4$ [17••]. Additionally, a second series showed an increased time to second recurrence for those who undergo a second surgery 29.7 versus 12.7 months, $p = 0.37$ [12]. Thus, if a patient presents with an isolated local recurrence, it may be worthwhile considering surgical resection.

In regards to chemotherapy, retrospective series and case reports have noted responses of locally advanced or metastatic adenosarcoma to chemotherapy, including doxorubicin/ifosfamide, liposomal doxorubicin, gemcitabine/docetaxel, and trabectedin, Table 4.

Table 3 Adjuvant chemotherapy for uterine adenosarcoma

Authors	Regimen	Cycles/dosing	No. of patients	Presence of sarcomatous overgrowth	Recurrence	Last reported status
Carroll et al. [17••]	Adj dox/ifosfamide	NR, NR	2	Yes	Yes	DOD
	Adj dox/ifosfamide	NR, NR	1	NR	No	Alive
	Adj cisplatin	NR, NR	1	No	Yes	NED
	Adj liposomal dox	NR, NR	1	NR	No	Alive
	Adj gem/doc	NR, NR	1	NR	No	Alive
	Adj Vinc/actin/cyclo	NR, NR	1	NR	No	Alive
Bernard et al. [18]	Adj dox/cisplatin	NR, NR	1	Yes	No	Alive
	Adj ifos/cisplatin	NR, NR	1	Yes	Yes	DOD
	Adj VAC-IE	NR, NR	1	Yes	No	Alive
	Neoadj dox/cisplatin	NR, NR	1	Yes	No	Alive
de Jonge et al. [82]	Adj dox/ifos, Adj ifos/cisplatin/etoposide	8, 50 mg/m^2/5g/m^2 3, NR	1	Yes	Yes	NED 57 months
Dincer et al. [83]	Adj, Anthracycline	NR, NR	1	Yes	NA	Progressive disease
Murugasu et al. [89]	Adj dox/ifos/carboplatin	6, NR	1	No	No	NED 2 years
Odunsi et al. [167]	Adj CyVADIC	9, 400 mg/m^2/2 mg/m^2/ 40 mg/m^2/800 mg/m^2	1	NR	No	NED 53 months
Huang et al. [168]	Adj ifos/cisplatin	2, NR	1	Yes	Yes	NED 18 months (After 6 cycles liposomal dox)
Guidozzi et al. [169]	Neoadj epirubicin/carbo	3, 80 mg/m^2/240 mg/m^2	1	NR	No	NED 52 months
	Neoadj epirubicin/carbo	3, 80 mg/m^2/240 mg/m^2	1	NR	No	NED 56 months
	Adj epirubicin/carbo	3, 80 mg/m^2/240 mg/m^2	1	NR	No	NED 34 months

Adj adjuvant, *Neoadj* neoadjuvant, *NR* not reported, *NA* not applicable, *DOD* dead of disease, *NED* no evidence of disease, *dox* doxorubicin, *gem/doc* gemcitabine/docetaxel, *ifos* ifosfamide, *VAC-IE* vincristine/doxorubicin/cyclophosphamide-ifosfamide/etoposide, *CyVADIC* cyclophosphamide/vincristine/doxorubicin /dacarbazine, *carbo* carboplatin

Table 4 Response to chemotherapy for recurrent or metastatic disease in uterine adenosarcoma

Authors	Regimen	Dosing	No. of patients	Response	Duration of response or survival
Yamagami et al. [170]	Doxorubicin/ifosfamide/cisplatin	50 mg/m^2 Dox Q3 weeks 50 mg/m^2 Cis Q3 weeks 7.5 g/m^2 Ifos Q3 weeks	3	1 PR 2 SD	2.6 months 1.5 months
Verschraegen et al. [171]	Gemcitabine/docetaxel/ bevacizumab	Gem 1500 mg/m^2 Q2 weeks Doc 50 mg/m^2 Q2 weeks Avastin 5 mg/kg Q2 weeks	1	1 PR	–
del Carmen et al. [172]	Liposomal doxorubicin	40 mg/m^2 Q4 weeks	1	1 PR	2 months
Huang et al. [168]	Liposomal doxorubicin	40 mg/m2 Q4 weeks	1	1 CR	18 months
Maeda et al. [173]	Liposomal doxorubicin	40 mg/m2 Q4 weeks	1	1 CR	–
Schroeder et al. [174]	Trabectedin	1.5 mg/m^2 Q3 weeks	3	2 PR 1 PD	13months, 8months –
Roman et al. [175]	Doxorubicin/ifosfamide/cisplatin	40 mg/m^2 Q4 weeks 4.5g/m^2 Q4 weeks 100 mg/m^2	1	PR	6 months
Carroll et al. [17••]	Doxorubicin/ifosfamide	–	3	2 PR 1 PD	21.8, 20.4, 13.7 months
	Doxorubicin/carboplatin (+surgery)	–	1	1 CR	
	Gemcitabine/docetaxel	–	2	1 PR 1 CR	31.9 months
	Doxorubicin/dacarbazine	–	2	2 PR	5.5 months, 62.8 months
	Doxorubicin	–	2	2 PD	10.1 month, 15.8 months
	Liposomal doxorubicin	–	1	1 PD	1.1 month, 6.7 months
	Carboplatin/paclitaxel (+surgery)	–	2	1 CR 1 PD	14 months
	Vin/doxorubicin/ifosfamide	–	1	1 CR	66.6 months, 3.9 months
	CyADIC (+surgery)	–	1	1 CR	16.5 months
	CyVADIC (+surgery)	–	1	1 CR	12.8 months 13.2 months
Tanner et al. [12]	Doxorubicin	–	1	1 PD	–
	Doxorubicin/ifosfamide	–	3	2 PR 1 PD	5.4 months, 9.1 month, –
	Doxorubicin/ifosfamide/cisplatin	–	1	1 PR	4.2 months
	Ifosfamide/paclitaxel	–	2	1 SD 1 PD	3.7 months
	Carbolatin/paclitaxel	–	1	1 SD	3.7 months
	Gemcitabine/docetaxol	–	2	1 PR 1 PD	2.4 months
	Ifosfamide	–	1	1 PR	3.9 months
Bernard et al. [18]	Doxorubicin/ifosfamide	–	1	NR	30 months alive
	Carboplatin/doxorubicin	–	1	NR	DOD 10 months
	Carboplatin/liposomal doxorubicin	–	1	NR	DOD 5 months
	Carboplatin/paclitaxel	–	1	NR	Still alive
	Cisplatin/bleomycin	–	1	NR	DOD 3 months
	Doxorubicin/cisplatin/cyclo	–	1	NR	DOD 2 months

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *mo* month, *DOD* dead of disease, *cyclo* cyclophosphamide, *vin* vincristine, *CyADIC* cyclophosphamide/doxorubicin/dacarbazine, *CyVADIC* cyclophosphamide/vincristine/doxorubicin/dacarbazine

However, there has been no prospective comparison of the efficacy and responses of these regimens in uterine adenosarcoma patients. The most pronounced and long-lasting responses appear to result from doxorubicin-containing regimens or gemcitabine/docetaxel. It is reasonable to consider these regimens in the treatment of patients with metastatic adenosarcoma. Furthermore, in the setting of an isolated local recurrence, it is reasonable to consider these regimens before surgery. Such an approach will allow assessment of tumor response to a specific regimen, and may help to improve treatment outcomes.

Conclusions

Adenosarcoma is a rare neoplasm of the female genital tract, occurring most commonly in the uterus. Patients without myometrial invasion and sarcomatous overgrowth may have acceptable outcomes with surgical resection alone. Prognosis is significantly worsened by the presence of myometrial invasion and/or sarcomatous overgrowth. Patients with adenosarcoma and sarcomatous overgrowth have a more aggressive disease with a shorter time to relapse, worse overall survival, and more local and distant recurrences. The standard of care treatment is surgical resection with total hysterectomy and bilateral salpingo-oophorectomy. Spread to regional lymph nodes is rare, so lymphadenectomy is not necessary unless there is a high clinical suspicion prior to resection. Adjuvant radiation therapy to the pelvis does not appear to improve overall survival. The role of chemotherapy in the adjuvant setting needs further investigation with specific regard to the choice of regimen and impact on survival. The most active regimens in the recurrent or metastatic setting are doxorubicin-based chemotherapy regimens or gemcitabine/docetaxel. Hormonal therapy can rarely lead to prolonged responses. Overall, there is limited evidence to guide treatment decisions in this rare disease, and clinical judgment of the treating oncologist must be utilized. Further research is required to help improve outcomes for patients with this rare disease.

Compliance with Ethical Standards

Conflict of Interest Michael J. Nathenson, Vinod Ravi, Nicole Fleming, Wei-Lien Wang, and Anthony Conley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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