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Prostate angiosarcoma: is there any association with previous radiation therapy?

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Abstract

For the current review a literature search was carried out using Pubmed, EmBase, and Cochrane databases. All cases of prostate angiosarcoma reported to date and observational studies evaluating the radiation associated cancer occurrence were reviewed. Despite the rarity, prostate angiosarcomas display remarkable clinical and pathological heterogeneity, and a treatment challenge. We found the association of prostate angiosarcoma with radiation therapy to be weak based upon the results from observational studies and case reports. Although radiation exposure has been suggested etiology of prostate angiosarcomas, assumption of such association is not supported by the current literature.

Keywords

prostate angiosarcoma; radiation therapy; adjuvant chemotherapy; multidisciplinary management

Sarcomas are malignant mesenchymal tumours. Angiosarcomas usually effect older individuals and encompass 2% of soft-tissue sarcomas. They frequently involve the skin, breast and soft tissue [1]. These very rare malignant neoplasms (only 10 identified in the current world literature) originate from the blood vessel endothelium and are distinguished by atypical, solid or multilayered endothelial proliferation [1]. In the present paper, we provide a review of prostate angiosarcomas, highlighting their epidemiology, aetiology, clinical presentation, histological features, prognostic factors and current treatment options.

EPIDEMIOLOGY

Rhabdomyosarcomas are the most frequent sarcomas of the prostate, accounting for >75% of cases, and are typically seen in infants, children and young adults [2,3]. Prostate angiosarcoma is an almost non-existent entity and the disease progression and prognosis of these tumours is poorly understood. A peak incidence has been noted between the ages of 40–50 and 70–80 years (mean age: 40 years) in the literature. One case even involved a 2-year-old child. Smith *et al.* [4] reported two cases and found two additional cases in the

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CONFLICT OF INTEREST

None declared.

literature from 1889 to 1986 [5,6]. Chan *et al.* [7] reported a fifth case of prostate angiosarcoma in a 35-year-old Chinese man, and Oliva Encina *et al.* [8] found a sixth case in a 31-year-old male. Chandan and Wolsh [9] reported the seventh case of angiosarcoma of the prostate in a patient who received radiation therapy for prostate adenocarcinoma 10 years earlier. Lee *et al.* [10] reported the eighth case, which was a 19-year-old male with prostate teratoma, resistant to chemotherapy, who was later found to have prostatic angiosarcoma. Guo *et al.* [11] found the ninth case of angiosarcoma in a patient who had undergone radiation therapy 4 years earlier. Khalik *et al.* [12] reported the 10th case, a 73-year-old man who had undergone external beam radiation therapy with brachytherapy boost for prostate adenocarcinoma 8 years previously and later presented with prostate angiosarcoma along with recurrent adenocarcinoma.

AETIOLOGY AND RISK FACTORS

Previous radiation exposure is a well-known risk factor for angiosarcomas. The direct oncogenic effects of ionizing radiation and prolonged cellular stimulation during repair of tissue damage resulting from radiation-induced ischaemic change are thought to play a role in the development of angiosarcoma [13]. Other factors that have been linked to angiosarcomas include: chronic lymphoedema and chemical exposure such as arsenic, thorium dioxide and vinyl chloride. None of the reported cases had a history of exposure to the above-mentioned chemicals.

Cahan *et al.* [14] proposed that radiation-induced sarcoma may occur in a previously irradiated area within a latent period of as long as 7 years. Although the association of angiosarcoma with radiation exposure has been described previously [15,16], only three out of 10 reported cases of prostate angiosarcoma had previous radiation exposure where PSA levels were within normal range or undetectable [9,11,12].

Only one of these three cases involved a recurrent adenocarcinoma of the prostate [12]. In the case report by Lee *et al.* [10], it was thought to be a malignant transformation within a pre-existing teratoma lesion; therefore, it is not clear whether post-radiation angiosarcoma stems from a dedifferentiated prostate cancer or signifies instead a second mesenchymal neoplasm. The estimated lifetime risk of developing post-irradiation sarcoma at any site with long-term follow-up appears to be 0.03% to 0.8% [17].

Huang *et al.* [18] reported an enhanced risk of soft-tissue sarcomas after adjuvant radiotherapy among patients with breast cancer in Surveillance of Epidemiology and End Results (SEER) data. This risk was especially increased for angiosarcomas and peak incidence was reported 5–10 years after the radiation therapy [18]. A concurrent lymphoedema, secondary to breast cancer treatment, was thought to be a potential confounder in this association [19,20]. A similar association between radiotherapy and subsequent angiosarcomas has also been reported in the gynaecological cancer literature [19,21]. Kim *et al.* [21] found 66 reported cases of radiation-associated angiosarcoma where the most common indication for radiation therapy was breast cancer (44%), followed by gynaecological cancer (21%). Kim *et al.* [21] also reported that 85% of radiation-associated angiosarcomas were detected in the skin with a median latency period of 8 years. In the same study, the median age at diagnosis was 65 years and median survival was 12 months [21].

Another large population-based cohort study evaluating the risk of angiosarcoma among all patients with cancer found an increased risk of truncal angiosarcoma among women with breast and gynaecological cancers [19]. This study did not find a strong relationship with radiotherapy, age or male gender. Although ionizing radiation is a well documented aetiology for angiosarcoma, Müller *et al.* [22] found no increased risk of secondary

malignancy in the literature from the mid-1980s to 2007 after adjustment for age and follow-up duration; however, they reported an enhanced number of secondary cancers of the bladder, rectum, lung and sarcoma after prostate irradiation.

Moon *et al.* [23] reported enhanced risk of second primary cancer of the bladder, rectum, gastrointestinal tract, brain and lung, lymphoma and leukaemia among patients with prostate cancer 5 years after radiation therapy as compared with those who did not receive radiation in SEER data. In the same study, men who received radiation therapy in the form of radioactive implants or isotopes did not have an increased risk of a second primary cancer [23]. In this large cohort study, no enhanced risk of prostate angiosarcoma was reported.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

Primary symptoms of prostate angiosarcoma include dysuria, haematuria and pain. Other reported symptoms are urinary frequency, decreased urinary stream, bladder spasm, constipation, weight loss, decreased libido, hematospermia and perineal pain (Table 1 [4-12]). Physical examination of the prostate was only significant or reported in four cases. Affected prostate glands were described as enlarged, firm, tender, boggy and containing a large solid mass. Diagnostic assessment was made using TURP in three cases, radical cystoprostatectomy in three cases, and incisional biopsy, rectal biopsy, and prostate biopsy in other cases. Seven out of 10 cases had no metastases and one case was lost to follow-up. One case had local metastases and one had metastases to the stomach, lung, spleen and liver. Three cases had a history of prostate adenocarcinoma with previous prostatic radiation therapy; however, serum PSA levels were either low or undetectable in those cases (Table 1).

PATHOLOGICAL FINDINGS

Although a hallmark of angiosarcomas is abnormal, pleomorphic, malignant endothelial cells, other variants that have been reported include: round, polygonal, fusiform or epithelioid cells [24]. In well-differentiated cancer, abnormal endothelial cells form vascular sinusoids dissecting between collagen bundles and are associated with monocyte infiltration. In aggressive disease, the tissue architecture becomes more chaotic, forming multilayered papillary projections in the vascular lumen. Mitotic bodies and cytoplasmic clusters of erythrocytes are also common in aggressive disease. In poorly differentiated tumours, areas of haemorrhage and necrosis among the continuous sheets of malignant endothelium impair the ability to differentiate these tumours from anaplastic carcinoma or melanoma [25]. Immunohistochemistry of the tumour is essential for diagnosis because angiosarcomas express endothelial markers like vascular endothelial growth factor (VEGF), *Ulex europaeus* agglutinin 1, factor VIII, CD31, and CD34. Factor VIII, *Ulex europaeus* agglutinin 1, and CD31 are the most useful markers in poorly differentiated angiosarcomas [26]. Among review of the reported cases, positive factor VIII staining was reported in five cases, positive CD34 staining in three cases, positive CD31 staining in three cases and positive vimentin in two cases (Table 1).

PROGNOSTIC FACTORS

Mortality was very high for prostate angiosarcoma in the reported cases (Table 1). Six patients died within 9 months of diagnosis; three were disease-free for a period of 16, 24 and 36 months; and one patient was lost to follow-up. Five-year survival is 50–60% for primary soft-tissue sarcoma [27] and 35% for angiosarcomas at any site [28-30]. Suspected poor prognostic factors for other soft-tissue sarcomas are tumour size (>5 cm) and grade, advanced age, visceral and retroperitoneal locations, metastases and poor patient performance status [25].

TREATMENT

Management of angiosarcoma is a challenge. The two most important determinants of treatment options are size of tumour and presence of metastases. The small number of cases and lack of clinical trials are the major limitations for site-specific angiosarcoma treatment recommendations. Treatment for prostate angiosarcoma follows the general guidelines for other soft-tissue sarcoma management as suggested by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). Although several vascular-targeted therapies are being tested in clinical trials, the present review focuses primarily on current available management. Among reported cases of prostate angiosarcomas, radical cystoprostatectomy was performed in six patients, whereas two patients had subtotal resections of the prostate (probably as palliative therapy only). One patient died shortly after hospitalization and one was lost to follow-up. Out of six cases where radical cystoprostatectomy was performed, clean surgical margins were only reported in one case. Three patients with radical cystoprostatectomy received adjuvant chemotherapy, consisting of doxorubicin in one case, experimental thalidomide in one case, and ifosfamide plus doxorubicin in the other. None of the reported cases received radiation therapy as a part of multimodal treatment because of suspected radiation-induced angiosarcoma.

LOCAL DISEASE

The primary treatment of choice for localized prostate angiosarcoma is radical surgery with complete (R0) resection and clean margins, but clean margins with R1 or R2 resection can sometimes be a challenge because of tumour size, tissue invasion, and relationship to adjacent critical organs, all of which confer poor prognosis [28,30-32]. Lahat *et al.* [33] reported improved survival among patients with recurrent angiosarcoma, who underwent surgery with pathological complete resection for localized disease. Although adjuvant radiotherapy with larger doses (>50 Gy) is generally recommended for treatment of sarcoma owing to the high risk of local recurrence, randomized radiotherapy trials have not been conducted. However, evidence from retrospective series suggests improved local control and overall survival with adjuvant radiotherapy [32]. Nevertheless, radiation therapy has not been recommended for radiation-induced angiosarcomas.

Use of adjuvant chemotherapy for risk reduction of metastasis in sarcoma has also been controversial owing to lack of clinical trials. Naka *et al.* [34] reported extended survival in patients who received adjuvant actinomycin-D after surgery although the number of patients was very small. We did not find prospective studies suggesting improved survival with the use of anthracycline-based adjuvant chemotherapy in soft-tissue sarcomas [25]. The only trial showing a survival benefit is the Italian and Scandinavian Sarcoma Groups study that focused on high-grade non-metastatic extremity osteosarcomas [35]. A meta-analysis of randomized controlled trials of adjuvant chemotherapy use for localized resectable soft-tissue sarcoma found an overall survival benefit only with combined doxorubicin and ifosfamide [36]. However, given the uncertainty surrounding this issue, the NCCN guidelines still recommend evaluating chemotherapy on a case-by-case basis. Use of chemotherapy for abdominal or retroperitoneal sarcomas has also not shown any survival benefit. Hence the use of chemotherapy in the neoadjuvant or adjuvant setting after definitive surgery for angiosarcoma remains controversial.

METASTATIC DISEASE

Cytotoxic chemotherapy with anthracyclines, ifosfamide, and taxanes has been the primary treatment for metastatic angiosarcoma. There are no evidence-based recommendations for treatment of metastatic prostate angiosarcoma because of small numbers of cases and associated comorbidities limiting use of chemotherapeutic agents. Use of combination

therapy has been associated with enhanced toxicity and failed to improve the overall survival [27]. The use of doxorubicin and ifosfamide as single agents has demonstrated response rates of 16–36% in soft-tissue sarcoma [27]. Taxanes have been viewed as promising therapy for treatment of angiosarcoma owing to their anti-angiogenic properties, but the response rates have been variable in other soft-tissue sarcomas [37,38].

There are a few case reports about thalidomide (an anti-angiogenic and immunomodulatory agent) use in advanced or metastatic angiosarcoma [39]. Other treatments with encouraging outcomes include the VEGF-A monoclonal antibody, bevacizumab [40] and interferon- α [41]. Sorafenib, a VEGF receptor small molecule inhibitor, has shown promising results against metastatic angiosarcoma [42]. Interferon- α , an immune modulator with anti-angiogenic activity has shown inhibition of transformed murine endothelial cell lines in preclinical studies [41]. There are also some case reports documenting a response to interferon- α in combination with doxorubicin for advanced cutaneous angiosarcoma [43]. Interleukin-2 has also been used as single agent, or in combination with chemotherapy or radiotherapy, suggesting that combined systemic and local treatment might improve survival [44]. Interferon- α and interleukin-2 use is currently not recommended for treatment outside clinical trials owing to insufficient data.

CONCLUSION

From a review of the literature, including both prospective and retrospective studies, we did not find a strong association between radiation therapy and prostatic angiosarcoma although this possibility cannot be excluded. Out of all the cases of prostate angiosarcoma, only three of 10 patients had a history of radiation therapy for prostate adenocarcinoma. Currently the main curative treatment method for prostatic angiosarcoma is wide surgical resection with clean margins. However, wide resection with clean margins can be a challenge because of the invasive nature of the tumour and proximity to critical organs. In addition, radiation therapy has never been used to treat prostatic angiosarcoma as recommended by general treatment guidelines for sarcoma by NCCN and ESMO. Despite a significant risk of subsequent metastatic disease, use of adjuvant chemotherapy for localized sarcomas or angiosarcoma is also not recommended as it has not shown any survival benefit. Based on available evidence, metastatic prostatic angiosarcoma can be treated with single-agent doxorubicin, paclitaxel, sorafenib or bevacizumab depending upon the functional status of the patient. At this time, patients should be offered participation in a clinical trial when available. Barring trial participation, patients should be referred to specialist centres where they can be managed by a team of radiation, medical and surgical oncologists.

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Abbreviations

SEER	Surveillance of Epidemiology and End Results
VEGF	vascular endothelial growth factor
ESMO	European Society for Medical Oncology
NCCN	National Comprehensive Cancer Network

What's known on the subject? and What does the study add?

Angiosarcomas are histological subtype of sarcomas and rarely involve the prostate gland. Only ten cases of prostate angiosarcoma have been reported in the literature to date. Occurrence of post-irradiation prostate angiosarcoma is rare considering the frequency of radiotherapy used for treatment of prostate adenocarcinoma. We provide a brief review of all cases of prostate angiosarcoma and describe the epidemiology, etiology, clinical presentation, histopathology, prognostic factors and current treatment options for prostate angiosarcoma.

TABLE 1

Case reports of prostate angiosarcoma in the literature

Case reports	Age, years	Symptoms	Metastasis	History of cancer or radiation exposure	Histopathology	Treatment	Clinical outcome
Botesco 1902 [5]	2	Dysuria and constipation	None	None	Numerous neoplastic blood vessels, degenerative connective tissue, lymphocytic infiltrate.	Died 1 day after hospitalization.	Died, 1 day
Salleras and Vilar 1924 [6]	32	Dysuria, constipation, and haematuria	None	None	Numerous vascular spaces with round or spindle, sometimes multinucleated, cells.	Lost to follow-up but terminally ill.	Lost to follow up
Smith <i>et al.</i> 1986 [4]	60	Reduced urinary stream and frequency	Local lymph node involvement	None	Solid sheets of round or pleomorphic cells with abundant cytoplasm. Enlarged, hyperchromatic, pleomorphic nuclei. Tumour cells lined slit-like spaces containing blood with prominent tufts. Factor VIII stain was positive.	Radical cystoprostatectomy with partial resection of pubic bone, ureteroleal diversion and bilateral pelvic lymph node dissection. Tumour extended to pelvic wall margin and was unresectable. 12 out of 22 lymph nodes were positive for metastases. Adjuvant chemotherapy not given because of poor functional status.	Died, 6 months
	42	Pain	None	None	Pleomorphic cells with elongated spindle. Nuclei varied from small and pyknotic to large and vacuolated with clumped chromatin containing one or more nucleoli. Rare vascular structures lined with malignant cells. Factor VIII stain positive. Pathology was consistent with poorly differentiated sarcoma with angiosarcomatous features.	Radical cystoprostatectomy with lymph node resection and ureteroleal diversion. Tumour resection was complete with clean margins, all lymph nodes free of tumour. Patient received adjuvant chemotherapy 2 months postoperatively with doxorubicin 70 mg/m ² followed by 3-week interval with 75 mg/m ² for total of six courses.	Disease free, 24 months
Chan 1990 [7]	35	Pain, haematuria, and urinary frequency	Lung, spleen, liver, and mesentery	None	Nodules of cellular and vascular tumour tissue in prostate. Vascular areas lined with neoplastic cells. Spindle-shaped with frequent mitosis. Positive staining for factor VIII and vimentin.	Developed haematuria after prostate biopsy, massive hemorrhage treated with CT embolization. Died from Disseminated intravascular coagulation (DIC), 4 days later.	Died, 5 weeks
Oliva Encina <i>et al.</i> , 2001 [8]	31	LUTS, urgency, dysuria, incomplete bladder	None	None	Epithelial angiosarcoma, infiltrating bladder and prostate.	Radical prostatectomy with partial resection of bladder neck and Ilio-obturator lymphadenectomy. Margins were not clean. Patient received adjuvant chemotherapy with six cycles of ifosfamide and	Disease free, 36 months

Case reports	Age, years	Symptoms	Metastasis	History of cancer or radiation exposure	Histopathology	Treatment	Clinical outcome
Chandan and Wolsh 2003 [9]	77	emptying, and decreased libido Gross haematuria, urinary frequency, dysuria, and spasm	None	History of prostate adenocarcinoma with Gleason score 7, treated with EBRT 10 years previously. PSA 0.0023 ng/mL (normal 0 = 0.04 ng/mL).	Staining positive for factor VII and CD21. Proliferating vascular channels lined by atypical endothelial cells surrounded by spindle-shaped cells. Tumour cells were pleomorphic with clumped chromatin and prominent nucleoli. Positive for factor VIII, CD34 and vimentin.	adriamycin plus radiation therapy. TURP, postoperative course complication by massive bleeding/haematuria and died 4 days later.	Died, 4 days
Lee <i>et al.</i> 2006 [10]	19	Dysuria, haematuria, and abdominal pain	None	History of immature teratoma. Serum α -fetoprotein 192 ng/mL (Normal <20 ng/mL) and β human chorionic gonadotropin 111.6 mIU/mL (Normal <5 mIU/mL).	Glands of variable size lined with either mature or immature intestinal, respiratory, and neuronal epithelia. Immature chondroid tissues, mature adipose tissues, and atypically proliferating endothelial cells with sporadic large, hyperchromatic nuclei, and frequent mitosis typical of intermediate grade angiosarcoma. Positive staining for CD31 and CD34.	Initially treated for immature teratoma with bleomycin, etoposide and cisplatin. However mass continued to grow, therefore underwent radical cystoprostatectomy with ileal conduit.	Disease free, 16 months
Guo <i>et al.</i> 2009 [11]	65	Haematuria and intractable perineal pain	None	History of prostate adenocarcinoma with Gleason score 3+3 = 6. Treated with androgen ablation and radiation 4 years previously. Serum PSA was undetectable.	Vasoformative growth with complex anastomosing channels. Tumour cells had highly atypical nuclei with robust mitotic activity. Positive staining for CD31 and CD34.	Total pelvic exenteration with positive margins.	Died, 8 months
Khaliq <i>et al.</i> 2012 [12]	73	Haematuria, nocturia and frequency	None	History of prostate adenocarcinoma with Gleason score 3 + 3 = 6. Treated with EBRT with brachytherapy boost 8 years previously. Serum PSA was 1.2 ng/mL (Normal range 0-4-5 ng/mL)	Proliferating vascular channels lined by atypical and malignant-appearing endothelial cells consistent with high grade angiosarcoma. The tumour cells stained positive for factor VIII and CD31. Tissue was extensively infiltrated by atypical large cells with active mitosis.	Total pelvic exenteration. Bladder and seminal vesicle involvement by direct tumour extension. At cystoprostatectomy, the tumour was present at the urethral margin and the left anterolateral pelvic sidewall. Surgical margins were positive for angiosarcoma and six out of nine pelvic lymph nodes were positive for metastatic prostatic adenocarcinoma with extranodal extension.	Died, 9 months

EBRT, external beam radiation therapy.