



## Primary Angiosarcoma of the Urinary Bladder: A Review of the Literature

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### Abstract

Primary angiosarcomas of the urinary bladder are very rare in view of this their clinical and pathological features have not been extensively described. Literature on primary angiosarcoma of the urinary bladder was reviewed performing an extensive search using various internet search engines for case reports, case series and review papers on primary angiosarcoma of the urinary bladder excluding metastatic angiosarcomas. Primary angiosarcomas of the bladder are rare tumours which are more commonly found in men and quite often present with haematuria, cystoscopy reveals raised lesions in the trigone / dome. Microscopic examination of the tumour tends to show anastomosing vascular channels lined by plump hyperchromatic cells as well as solid and epithelioid cytology. Typically the tumour is locally invasive invading the muscularis propria. The tumour stains positively with CD31, CD34 and can be focally positive especially in cases of epithelioid tumours. Few cases have so far been reported and on the whole previous reports have indicated poor prognosis. However, recent anecdotal reports have indicated that multi-modality treatment with radical cystectomy and adjuvant combination chemotherapy and radiotherapy may result in long term survival. Primary angiosarcomas of the urinary bladder tend to affect middle-aged and elderly men. Anecdotal reports have indicated longer term survival with multi-modal treatment strategy unlike previous reports which on the whole indicated poor prognosis. There is no consensus opinion regarding their treatment. There is therefore the need for a multi-centre trial to determine the best treatment options that would improve the prognosis for these tumours.

**Key Words:** Primary Angiosarcoma, Urinary Bladder, Radiation-induced sarcoma, CD31, CD34, Immunohistochemistry.

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### Introduction

Majority of vascular lesions in the urinary bladder are haemangiomas which comprise 0.6% of all urinary bladder cancers and this makes primary

angiosarcoma of the urinary bladder very rare. [1] The first case of angiosarcoma of the urinary bladder was apparently described by Jungano in 1907 [2], although Jungano referred to an older report from 1905 of a “telangiectatic fibrosarcoma” of the bladder in a 64-year-old man, which by modern criteria may have truly been the first case of angiosarcoma of the urinary bladder. [3] In view of the rarity of angiosarcomas of the urinary bladder, the biological behaviour of these tumours, have not been clearly / extensively clarified. Furthermore, the pathological features of primary angiosarcomas of the urinary bladder have not been well described and as a result, establishment of a diagnosis of primary angiosarcoma of the urinary bladder may be extremely difficult to render. [3]

The ensuing paper contains a review of the literature on primary angiosarcoma of the urinary bladder.

### Methodology

Various internet search engines were used to search extensively for case reports, case series and review papers on primary angiosarcoma of the urinary bladder which were used to ascertain the presentation, investigation, diagnosis, management and outcome of patients following treatment.

### Overview

Angiosarcoma of the urinary bladder is a rare vascular tumour with anastomosing vascular channels in which endothelial cells are seen to exhibit marked cytologic atypia.[4]

*Epidemiology:* Angiosarcoma of the urinary bladder is more common in the male with 89% occurrence. The mean age of occurrence of this tumour is 64%. [4]

*Aetiology:* A number of factors have been associated with the development of angiosarcoma of the urinary and these include:

- Radiotherapy for pelvic malignancy in 1 out of 3 cases [4]
- Exposure to arsenic [4]
- Exposure to thorium chloride[4]
- Exposure to polyvinyl chloride [4]
- Exposure to chemotherapeutic agents [4]

Angiosarcoma of the urinary bladder had been reported in bladder with pre-existing haemangioma. [4]

*Presentation:* Angiosarcoma of the urinary bladder usually presented with haematuria. [4]

*Macroscopic Appearance:* Angiosarcoma of the urinary bladder typically is seen as haemorrhagic raised mass with a mean diameter of about 7 cm of the trigone or dome. [4]

*Microscopic Appearance:* Microscopic examination of angiosarcoma of the urinary bladder typically shows the following features: Anastomosing vascular channels which are lined by plump hyper-chromatic cells, as well as solid growth and epithelioid cytology. Typically the tumour invades the muscularis propria (see figures 1 – 3). [5]

*Immunohistochemical staining characteristics:* Angiosarcoma of the urinary bladder on immunohistochemistry stain positively with:

- CD31 [4]
- CD34 [4]
- Cytokeratin can be focally positive, especially in cases of epithelioid tumours. [4]

*Differential Diagnosis:* The differential diagnosis of angiosarcoma of the urinary bladder, include the following:

**Haemangioma** – It is typically 1 cm or less, 80% are cavernous, exhibits no atypia, not associated with anastomosing or solid areas. [4]

**Kaposi's sarcoma** – It is associated with Human Immunodeficiency virus (HIV) and HHV8, presence of extravasated red blood cells, usually associated with less atypia than angiosarcoma. [4]

**Sarcomatoid variant of urothelial carcinoma** – It exhibits undifferentiated spindle cells, has an associated urothelial carcinoma, vascular markers are negative in it. [4]

*Treatment:* Treatment of angiosarcoma of the urinary bladder is by wide resection and perhaps radiotherapy and chemotherapy may have a role. [4]

*Prognosis:* Traditionally angiosarcoma of the urinary bladder has been considered to be associated with poor prognosis. However, Seethala et al. [3] recently indicated that their prognosis may be better than previously conjectured. [3] Furthermore, survival 6 years after initial presentation has been reported recently. [6]

### Narrations from case reports, case series and reviews

Pazona et al. [6] reported the long-term disease free survival of one patient who was treated by means of multi-modal therapy whom they had previously reported on. Six years, pursuant to the patient's initial presentation, the patient died and the post-mortem examination no evidence of residual disease. They stated that their case represented the longest reported survival of a patient with angiosarcoma of the urinary bladder. [6]

Seethala et al. [3] reported that based upon the context that primary angiosarcoma of the urinary bladder is extremely rare and their clinical and pathologic features had not been well described, they identified relevant sources using MEDLINE and a subsequent bibliographic search of all case reports and reviews on primary angiosarcoma of the urinary bladder. They also searched the M.D. Anderson centre pathology archives. Seethala et al, [3] extracted data on the following demographics: clinical presentation, predisposing factors, gross pathology, microscopic pathology, immunophenotype, therapy, and outcomes. Seethala et al, [3] stated that:

- Primary bladder angiosarcoma was found at a mean age of 64.2 years, with a male to female ratio of 8:1.

- Two cases arose in a post-irradiation setting.
- Primary bladder angiosarcoma typically presented with haematuria and were grossly-haemorrhagic -raised masses (mean size 6.7 cm), of the trigone / and of the dome.
- Histologically, most of the tumours exhibited classic anastomosing channels lined by plump hyperchromatic cells, although many exhibited variant histology such as solid growth and epithelioid cytology.
- Three (43%) of 7 patients died within a year, but only 1 patient with evidence of disease. The remaining patients were alive at the time of publication of their respective cases (mean, 22 months).

Seethala et al. [3] concluded that primary angiosarcomas of bladder are typically rare tumours of middle-aged and elderly men that present with locally advanced disease and show a wide histologic spectrum. However, their prognosis may be better than previously thought.

Tavora et al. [5] retrospectively identified vascular tumours of the urinary bladder from the consultation files from one of the authors. They identified 13 lesions which included 3 haemangiomas, 3 intravascular papillary endothelial hyperplasias (Masson vegetant haemangioendotheliomas), 2 arteriovenous malformations (AVMs), 1 epithelioid haemangioendothelioma (EHE), and 4 angiosarcomas. Tavora et al. [5] stated that:

- One of the angiosarcomas was associated with conventional high-grade urothelial carcinoma (sarcomatoid variant of urothelial carcinoma).
- All the patients were adults with a range in age from 18 to 85 years old (mean 63.3).
- There was no statistical difference among the various lesions in terms of age, although angiosarcomas tended to arise in older patients (mean 71 y vs. 60 y of the remainder).
- Haematuria was the most common presentation of both benign and malignant lesions.
- Some of the other symptoms included voiding irritation, pelvic pain, and obstruction.
- Histologically, benign and malignant lesions were similar to their counterparts in other organ systems.
- Two haemangiomas were of the capillary type and a third one of the cavernous sub-type. They measured 1.1 cm, 2.4 cm, and 3.2 cm.
- Both arteriovenous malformations (AVMs were) clinically large broad-based masses which

measured 5.5 cm and 5.8 cm in greatest diameter. One of the arteriovenous malformations (AVMs) was associated with pseudo-epitheliomatous hyperplasia of the urothelium.

- All of the 3 patients with Masson lesion had history of radiation therapy for other causes. These presented as raised lesions and they were all <1.0 cm.
- Patients with haemangiomas, papillary endothelial hyperplasias, and arteriovenous malformations (AVM) had an invariably benign prognosis and they needed no further therapy. These benign lesions had consistent involvement of the sub-mucosa and spared the muscularis propria of the organ.
- All the cases of angiosarcoma and epithelioid haemangioendothelioma (EHE) involved the muscularis propria.
- Two of four patients with angiosarcoma had a history of prior radiation therapy and all the four patients were dead of disease at 6 months.
- The angiosarcomas measured 3 cm, 4.5 cm, 5 cm, and 5.8 cm in greatest diameter at cystoscopy.
- The patient with epithelioid haemangioendothelioma (EHE) had a single nodule which was treated by trans-urethral resection of the bladder lesion and no evidence of disease at 4 years of follow-up was found.
- None of the patients experienced marked visible haematuria that resulted in morbidity or mortality.
- A wide spectrum of benign, intermediate-malignant, and malignant vascular lesions primarily involved the bladder.
- Despite the potential for marked haemorrhage, none of the tumours resulted in marked haematuria.

They concluded that papillary endothelial hyperplasia occurs in the bladder and must be differentiated from angiosarcoma, which has a rapidly fatal outcome. Kulaga et al. [7] in 2007, reported a woman who developed epithelioid angiosarcoma of the urinary bladder which she developed after she had received radiation treatment for endometroid adenocarcinoma. [7]

In 2008, Williams et al. [8] reported a 71-year-old man, who presented with a single episode of visible painless haematuria. He had undergone external beam radiotherapy for prostate cancer 10 years

earlier. His clinical examination revealed a palpable left pelvic mass. He had a computed tomography (CT) scan which confirmed the presence of a left-sided bladder wall mass with unilateral hydronephrosis. At cystoscopy the tumour was found to arise from the left hemi-trigone, and bimanual examination under anaesthesia revealed a mass which appeared to be fixed to the pelvic sidewall. A trans-urethral resection of the tumour was undertaken and a left indwelling ureteral stent was placed. Histological examination of the resected specimen was consistent with epithelioid angiosarcoma infiltrating the muscularis propria. Subsequently, the patient underwent a radical cystoprostatectomy, pelvic lymph node dissection, and construction of an ileal conduit. Intra-operatively, there was a large extravesical mass which extended to and invaded the pelvic sidewall. A wide resection was carried out, which revealed no residual gross tumour behind. The pathological examination revealed a mass with mucosal ulceration. The lesion involved the bladder wall and invaded through the detrusor muscle. It also involved the perivesical soft tissue, prostate, and seminal vesicle (see Fig. 4).

The patient recovered from surgery, and was referred for adjuvant chemotherapy and radiotherapy. Despite a reasonably good appetite, he continued to lose weight post-operatively. He developed malignant ascites and bilateral lower extremity oedema. He had a repeat computed tomography (CT) scan 2 months following surgery which revealed diffuse carcinomatosis. The patient subsequently opted for hospice care and died 3 months post-operatively.

Williams et al. [8] stated that:

- Very little is known regarding the natural history, optimal treatment, and prognosis of renal angiosarcomas.
- Engel et al. [9] reported on 10 cases with angiosarcoma of the bladder]. They found an almost universally poor prognosis, with an overall mean survival of only 8.5 months.
- Mark et al. [10] iterated that these tumours are usually high-grade and they have a reported 5-year survival rates of between 10 and 35%.
- At the time of the report of their case, 13 cases of bladder angiosarcomas had been reported. Three of these patients had an antecedent history of pelvic radiotherapy. Two cases were reported after radiation therapy for a gynaecologic

malignancy [11], [12] while one appeared after therapeutic irradiation for prostate cancer [13].

- None of these patients had an antecedent history of exposure to arsenic, thorium dioxide, or vinyl chloride.
- The most common presentation of these patients was haematuria [3], while dysuria and flank pain were less common symptoms.
- There was a marked male predilection, with reports of male to female ratio of 8:1.
- The tumours tended to arise from all areas of the bladder. As with most sarcomas, the lung and the liver were common sites for metastases, with a haematogenous metastatic pattern the rule.
- The development of a secondary malignancy is a recognized risk of radiation therapy as reported by a number of authors [9], [11], [13], [14].
- In considering the diagnosis of a radiation-induced sarcoma, Cahan et al. [15] suggested the following criteria: (1) the sarcoma should arise in the area previously subjected to irradiation, (2) a latent period (at least 7 years) must exist between the time of irradiation and development of the sarcoma, and (3) the sarcoma must be confirmed histologically. [15]
- The association of angiosarcoma with therapeutic radiation has been previously described [11], [13].

Williams et al. [8] furthermore, stated that:

- Their reported case satisfied all of the aforementioned criteria and, thus, could be considered radiation related.
- In addition to the direct oncogenic effect of ionizing radiation, prolonged cellular stimulation during repair of tissue damage resulting from radiation-induced ischemic change may play a role in development of angiosarcoma [16]
- The management of these patients is surgical resection of the tumour with generous circumferential margins whenever possible. Radical cystectomy and ileal conduit was performed on this patient. Negative margins are crucial for cure and improved local control has been demonstrated in high-grade lesions with adjuvant radiotherapy [10].
- Mark et al. [10] reported an actuarial disease-free survival of 43% when adjuvant radiotherapy was given in angiosarcomas compared to 17% without. In general, randomized trials have failed to show a survival benefit for chemotherapy in the treatment of soft-tissue sarcomas [17].

- Multimodal approaches with chemotherapy and radiotherapy had shown promising results in high-grade sarcomas of the head and neck [18]
- Pazona et al. [6] reported on long-term survival after multimodal therapy for bladder angiosarcoma. They reported on a patient treated with radical cystectomy with adjuvant chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) followed by pelvic irradiation. The patient died of a cardiac event 6 years after surgery with no evidence of disease at autopsy.
- Likewise, Engel et al. [9] reported on a patient with primary angiosarcoma of the bladder who was treated with combined cystectomy, MAID chemotherapy, and external beam radiation. They reported that at 32 months after diagnosis and initial treatment, the patient had no evidence of disease.

Williams et al. [8] stated that their patient had rapid disease progression after surgery, and was therefore not a candidate for adjuvant therapy. Williams et al. [new 8] [6] concluded that:

- Angiosarcoma of the bladder is an extremely aggressive tumour with a short disease course.
- If an attempt at cure is feasible, a multi-modal approach consisting of radical surgery followed by high-dose adjuvant radiotherapy and chemotherapy would seem most effective.

Warne et al, [19] reported a 32-year-old woman who presented initially with left flank pain and visible haematuria throughout her urinary stream. She had computed tomography scan of her kidneys, ureter and urinary bladder (CT KB) which revealed ureteric dilatation down to the level of the bladder without evidence of renal calculus. She subsequently underwent insertion of left ureteric stent. She re-presented a month later with contra-lateral flank pain and a trans-urethral resection of bladder tumour was performed. Histopathological examination findings were consistent with a diagnosis of angiosarcoma. Magnetic resonance imaging (MRI) scan of the pelvis was done which revealed that the tumour arose from the posterior wall of the urinary bladder with local invasion and regional lymph node metastasis. Ifosfamide and epirubicin chemotherapy, with single-fraction radiotherapy induced significant reduction in tumour bulk, though the initial response was ensued by symptoms suggestive of disease progression. She died 19 months after initial

diagnosis with persistent pulmonary and vertebral metastases, though autopsy was not performed.

Ravi [20] reported the case of primary angiosarcoma of the urinary bladder in a man who did not have exposure to any aetiological factors and who was disease free 8 months after he had undergone partial cystectomy and adjuvant post-operative pelvic irradiation.

Engel et al. [9] reported a case of angiosarcoma of the bladder, and they reviewed 9 other previously reported cases. Engel et al. [9] stated that of the 10 cases, 2 were considered to have arisen from a pre-existing bladder haemangioma. Two patients had a history of prior gynaecologic malignancies treated with external beam radiotherapy, with subsequent sarcoma formation within the past treatment field. Two other patients presented with skin lesions that predated the discovery of bladder lesions. Only 4 patients presented with primary bladder lesions and no pre-existing disease or previous carcinogenic exposure (except for tobacco use). Haematuria was a universal presentation, and treatment was widely-variant. Of the 10 patients, 8 died during a period of follow-up of 23 months. Five patients died of tumour-related causes. Mean survival of these 5 was 10.6 months. The 2 most recent patients (including ours) were alive and tumour free at 8 and 32 months, respectively. Both of these patients underwent multimodality oncologic approaches as part of their treatment regimen.

Engel et al. [9] concluded that:

- Angiosarcoma of the bladder is exceedingly rare and usually fatal.
- Prognosis is poorer than that of angiosarcomas in more traditional sites.
- Regional lymph nodes are typically spared, but local recurrence with eventual distant metastasis is the rule. Optimal therapy has not been determined, but it most likely should involve a multimodal approach combining radical surgery with chemotherapy and radiotherapy.

Aragona et al [21] in 1991 reported the second case of primary angiosarcoma of the bladder and they pointed out the immunohistochemical characteristics of these neoplasias. They stated that using immunoperoxidase staining techniques, Ulex lectin had proved to be a more sensitive marker for endothelial cells than factor VIII-related antigen, and

that it should be used as an additional marker for endothelial cell-derived tumours. Schindler et al. [22] also reported a 47-year-old man who had angiosarcoma of the urinary bladder.

Spiess et al. [23] assessed the histologic subtypes, clinical presentations, treatment approaches, and treatment-related outcomes of patients with bladder sarcoma. They stated that between January 1985 and July 2004, 19 patients (12 men and 7 women) with primary bladder sarcoma were evaluated at the University, of Texas M.D. Anderson Cancer Centre. Median follow-up duration was 72 months (range 3-141). Spiess et al. [23] reported that:

- The median age of patients at presentation was 57 years (range 22-94). The histologic subtypes of bladder sarcoma were leiomyosarcoma (N = 14), angiosarcoma (N = 3), and unclassified sarcoma (N = 2).
- The clinical presentation consisted of gross, painless haematuria in 79% of patients, lower urinary tract symptoms in 16%, and microhematuria in 5%.
- The primary treatment modalities used were surgery in 16 (84%) patients, chemotherapy in 2 (11%), and palliation in 1 (5%).
- The rate of local and distal recurrence was 16% and 53%, respectively. The most common sites of distant metastases were the lungs, bone, brain, and liver. The 5-year disease-specific survival rate was 59%, with the median- survival duration of 6 years. There was no statistically significant difference in disease-specific survival between patients with bladder leiomyosarcoma compared to other sarcoma subtypes (P = 0.149).
- Lymphovascular invasion (P = 0.03) and lymphatic metastasis (P = 0.03) were associated with disease-specific survival, and surgical margin status was associated with recurrence-free (P = 0.04), disease-specific (P = 0.03), and overall survival (P = 0.005).

Spiess et al. [23] concluded that: Bladder sarcoma is a highly aggressive malignancy, regardless of its histologic subtype. Surgical margin status is an important determinant of survival.

The development of a secondary malignancy pursuant to radiotherapy has been recognized as a risk of radiation therapy. [8] [9] [11] [13] [14]. In the consideration of the diagnosis of a radiation induced sarcoma, Cahan et al. [15] postulated the ensuing criteria:

- (1) The sarcoma should arise in the area previously subjected to radiation.

- (2) A latent period (of at least 7 years) must exist between the time of the irradiation and the subsequent development of the sarcoma.

- (3) The sarcoma must be confirmed histologically. Some authors [11] [13] had previously reported the association between angiosarcoma and radiotherapy (therapeutic radiation).

Chen et al. [16] iterated that in addition to the direct oncogenic effect of ionizing radiation, prolonged cellular stimulation during the process of tissue damage which follows radiation-induced ischaemic change may have a role to play in the development of angiosarcoma.

Williams et al. [8] stated that the management of patients with angiosarcoma of the urinary bladder is surgical resection of the tumour with generous circumferential margins whenever possible. It has also been stated that negative surgical margins are crucial for cure and improved local control had also been demonstrated in high-grade lesions with adjuvant radiotherapy. [10]

Williams et al. [8] provided the ensuing statements which in the author's view should be taken into consideration when planning the treatment of angiosarcoma of the urinary bladder:

- Mark et al. [10] had earlier on reported an actuarial disease-free survival of 43% when adjuvant radiotherapy was given in angiosarcomas in comparison with 17% without adjuvant radiotherapy.
- Generally, results of randomized trials had failed to show any survival benefit for chemotherapy in the treatment of soft-tissue sarcomas. [17]
- Colville et al. [18] had reported that multi-modal approaches with chemotherapy and radiotherapy had shown promising results in high-grade sarcomas of the head and neck.
- Pazona et al. [6] had reported on a patient who underwent radical cystectomy with adjuvant chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine [MAID]) which was followed by pelvic irradiation. The patient died of a cardiac event 6 years later with no evidence of disease at autopsy which evidenced long-term survival.
- Engel et al. [9] reported on a patient who had angiosarcoma of the urinary bladder and was treated by means of combined cystectomy, MAID chemotherapy, and external beam radiotherapy. Engel et al. [9] reported that at 32 months following diagnosis and initial treatment, the patient had no evidence of disease.

- Tables 1 and 2 contain a summary of some of the reported cases of angiosarcoma of the urinary bladder.

**Table 1:** Clinical parameters of Primary Bladder Angiosarcoma [...indicate information not available]

Source & year	Age / Sex	Predisposing factors	Clinical presentation
Jungano 1907 [2]	54 / M	.....	Obstruction & intermittent haematuria
Casal et al. 1970 [24]	85 / F	“”””	Haematuria; dysuria; weight loss
Stroup & Chang 1987 [25]	68 / M	.....	Haematuria
Aragona et al. 1991 [21]	78/M	.....	Haematuria & visible haematuria
Ravi 1993 [20]	55/M	“”””	Intermittent painless haematuria
Navon et al. 1997 [13]	78/M	Radiation 13 years prior to diagnosis	Single episode of painless haematuria
Engel et al. 1993 [9]	47/M	.....	Haematuria; left flank and groin pain
Schindler et al. 1999 [22]	47/M	....	Dysuria; left flank pain
Seethala et al 2006 [3]	65/M	Radiation 4 years prior to diagnosis	Visible painless haematuria
Pazona et al. [6]	...	.....	...
Kulaga et al. [7]	F	Previous radiation for endometriod carcinoma	....
Williams et al. 2008 [8]	71/M	External beam radiotherapy 10 years earlier	Single episode of gross haematuria
Morgan et al. 1989 [12]	F	Previous radiation	
Warne et al. 2011 [19]	32/F	...	Loin pain & haematuria
Spies et al. 2007 [23]	3 cases ages and sex... cases reported together with other sarcomas totalling 19	...	Haematuria most of the patients
Abbasov et al. 2011 [26]	...	...	...
Tavora et al. 2008 [5]	4 cases Mean age 71 years	2 out of 4 had history of prior radiotherapy	Haematuria ...

**Table 2:** Pathological parameters for Primary Bladder Angiosarcomas

Source, year	Gross/cystoscopy	Site	Size cm	Depth of invasion	Architectural patterns	Cytologic features	Mitotic rate	Immunophenotype
Jungano 1907 [2]	Large sessile, with extensive clots	Right trigone and ureteric orifice	...	....	Classic, focally with large dilated vascular spaces	Typical and spindled	...	...
Casal et al. 1970 [24]	Vegetative haemorrhagic	Left ureteric orifice	3	...	Classic focally solid	Bland + and typical	High	...
Stroup & Chang 1987 [25]	Raised erythematous nodule	Dome	1	At least lamina propria	Classic ±	Typical±	6/10 HPF	FVIII+, cytokeratin-
Aragona et al. 1991 [21]	Round exophytic mass with foci of haemorrhage	Left bladder diverticulum	7	Perivesical fat near left seminal vesicle (LSV)	Classic	Typical and high spindled	High	Factor VIII-related antigen (FVII+), Ulex europaeus antigen 1 (UEA1+), cytokeratin-, desmin-, myoglobin-, vimentin-, S100-, Leu-7-
Ravi 1993 [20]	Vascular solid mass	Dome	10	Muscularis propria	Classic	Typical	...	...
Navon et al. 1997 [13]	Erythematous nodule.	Trigone	...	Perivesical fat	Classic	Typical	Rare	CD34+, FVIII+, and UEA1-
Engel et al. 1998 [9]	Diffuse erythematous hard lesion with associated haemorrhage and clots	Left trigone	4.9	Perivesical fat	Solid and primitive	Epithelioid	...	...
Schindler et al. 1999 [22]	Erythematous bleeding lesion	Left lateral wall and trigone	...	...	Solid, focally classic	Epithelioid	...	CD31+, vimentin+, CD34-, FVIII-, cytokeratin-
Seethala et al. 2006 [3]	Indurated haemorrhagic necrotic lesions	Diffuse, Left side, posterior wall and dome predominant	14	Peritoneal surfaces	Solid, focally primitive	Epithelioid and spindled	5/10 HPF	CD31+, CD34+, cytokeratin-
Williams et al 2008 [8]	Left sided bladder mass and bimanual examination revealed mass fixed to pelvic side wall	Left hemi-trigone	...	Extended through the detrusor muscle and beyond and fixed to pelvic side-wall	Classic	Some atypical endothelial cells	...	CD31+ (positive)
Morgan et al. 1989 [12]	...	...	...	...	...	Also involved vagina	...	...
Warne et al. 2011 [19]		Posterior wall of bladder causing hydroureter, left and right		Locally invasive plus lymph node metastasis		Histology consistent with angiosarcoma	...	...

Spies et al. 2007 [23]	...	...	...	...	...	...	...
Abbasov et al. 2011 [6]	...	...	...	...	...	...	...
Tavora et al. 2008 [5]	...	3 4.5 5 5.8	All cases classic involved Muscularis propria at least	1 was associate with sarcomatoid variant of conventional urothelial carcinoma	...	...	...

**Table 3:** Treatment and follow-up for Primary Bladder Angiosarcomas

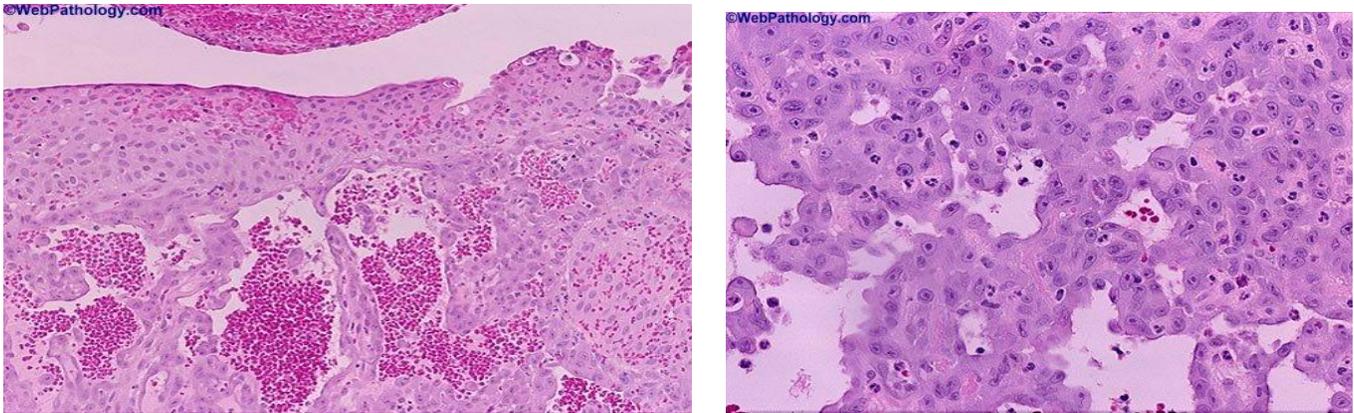
Source, year	Primary treatment	Final Margins	Additional Treatment	Local Recurrence	Metastases	Outcome
Jungano 1907 [2]	Resection of tumour	Incomplete resection of tumour	Unknown	...	...	...
Casal et al. 1970 [24]	Partial cystectomy	...	None	...	...	Died 3 days after diagnosis from myocardial infarction, no autopsy
Stroup & Chang 1987 [25]	TURBT	Incomplete TURBT	None	1	Multiple lung and liver nodules	Died 8 months after diagnosis from myocardial infarction; autopsy showed lung and liver metastases
Aragona et al. 1991 [21]	Partial cystectomy (diverticulectomy)	Negative	None	...	...	Died 2 months after diagnosis from myocardial infarction; no clinical evidence of disease; no autopsy
Ravi 1993 [20]	Partial cystectomy	Negative	Adjuvant radiotherapy to pelvis to 5500 cGy	...	...	Alive and well 8 months after diagnosis
Navon et al. 1997 [13]	Cystoprostatectomy	...	None	...	...	Alive and well 30 months after diagnosis
Engel et al. 1998 [9]	Cystoprostatectomy	Positive	MAID (5 cycles) radiotherapy to pelvis to 5940 cGy boost to right groin to 6420 cGy	...	Right inguinal lymph node	Alive and well 29 months after diagnosis
Schindler et al. 1999	Cystoprostatectomy	...	None	1 + (not biopsy)	Right inguinal	...

[22]				proven)	lymph node	
Seethala et al. 2006 [3]	Cystoprostatectomy	Positive	Gemcitabine and docetaxel (5 cycles)	...	Peritoneal+	Alive and well 19 months after diagnosis
Pazona et al. [6]	Multi-modal treatment Radical cystectomy & adjuvant chemotherapy followed by pelvic irradiation		Multi-modal treatment Adjuvant chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine [MAID] followed by pelvic irradiation	None	None	Died 6 years later of a cardiac event autopsy revealed evidence of residual disease
Williams et al. 2008 [8]	TURBT; radical cystoprostatectomy, pelvic lymph node dissection, ileal conduit, wide resection of extra-vesical mass that extended to and invaded pelvic side wall revealing no residual gross tumour behind tumour involved the bladder wall, through detrusor, perivesical soft tissue, prostate, and seminal vesicle stage T4 tumour	Would be deemed incomplete (from description)	Was referred for adjuvant chemotherapy and radiotherapy but did not have the chance to have the treatment	Yes with bilateral lower extremity oedema	Malignant ascitis	Died 3 months post-operatively in hospice
Warne et al. 2011 [19]	TURBT	Residual disease in pelvic node	Ifosfamide and epirubicin chemotherapy and single-fraction radiotherapy	initial reduction in tumour bulk tissue biopsy not done	Pulmonary and vertebral metastases persisted despite initial reduction in tumour bulk tissue biopsy not done	Died of disease metastases 19 months after diagnosis
Tavora et al. 2008 [5]	...	...	...	...	...	All 4 were dead of disease at 6 months

**Summary of abbreviations;** ... indicate details not available; TURBT, trans-urethral resection of bladder tumour; RT, radiotherapy; MAID, mesna, doxorubicin (Adriamycin), ifosfamide, and dacarbazine. + Not biopsy proven, based on imaging studies.

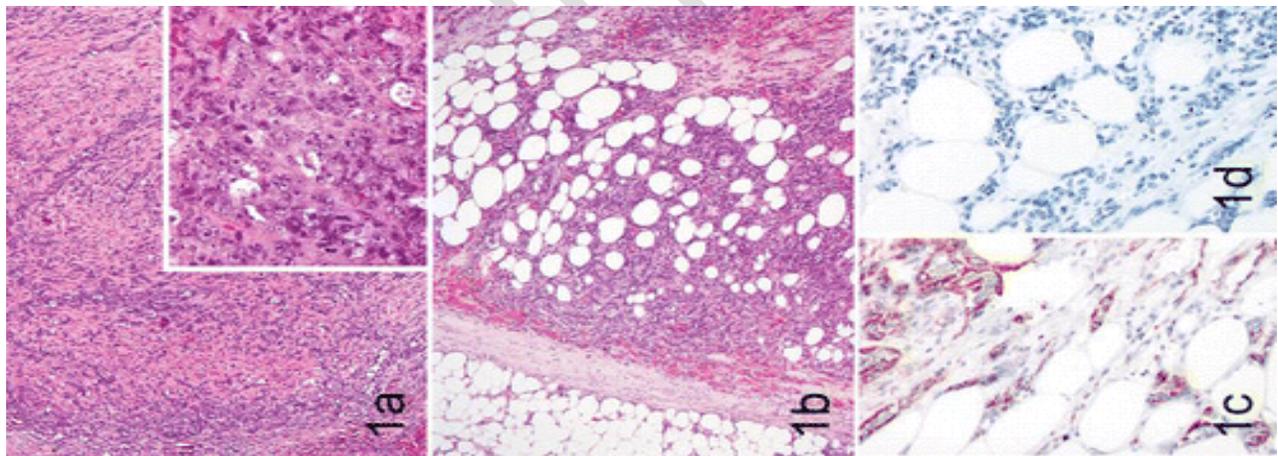
**Figure 1:** This bladder biopsy shows anastomosing vascular channels lined by atypical endothelial cells just beneath the normal endothelial lining (reproduced with copy right permission from web pathology.com and pathology outlines .com)

**Figure 2:** The atypical endothelial cells have large vesicular nuclei with prominent nucleoli. The prognosis of vesical angiosarcoma is grim Arch Esp Urol 1993 May; 46(4): 351 – 353 Reproduced from pathology outlines.com / webpathology.com with permission from both



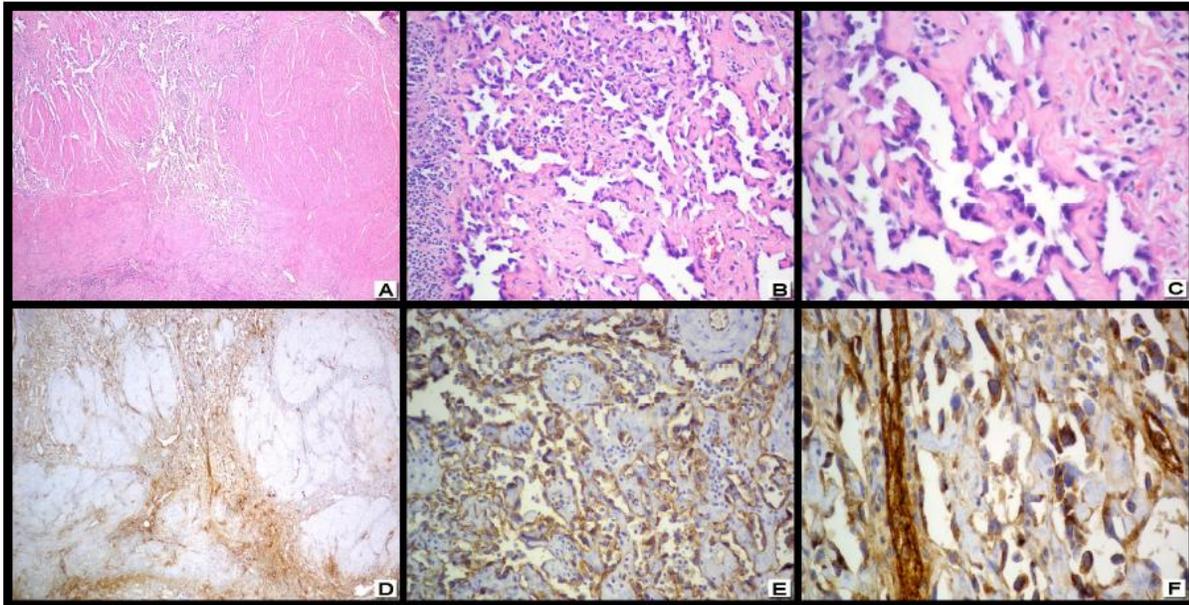
**Figure 3:** a. A predominantly solid growth pattern in an angiosarcoma infiltrating the muscularis propria of the bladder (haematoxylin and eosin staining original magnification x 40) inset; The tumour has an epithelioid cytology with focal formation of lumina filled with red blood cells (haematoxylin and eosin staining original magnification x 200)  
 b. Angiosarcoma with primitive capillary-size tubules infiltrating into the perivesical adipose tissue (haematoxylin and eosin staining original magnification x 40).The same tumour is immunohistochemically positive for CD31 (c. original magnification x 100) and negative for cytokeratin (d. original magnification x 100), confirming the diagnosis of angiosarcoma.

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 As well as: [3] Seethala R, R, Gomez J A, Vakar-Lopez F. Primary angiosarcoma of bladder. *Arch Pathol Lab Med* 2006 Oct; 130 (10): 1543 – 1547 with copy right permission from the Editor in chief of the Journal on behalf of the journal.



**Figure 4:** (A–C) Haematoxylin-eosin stained sections at 10, 20, and 40 $\times$ , respectively, showing the bladder wall invaded by a vascular tumour, in which vascular channels are lined by atypical endothelial cells. (D–F) CD31 staining at 10, 20, and 40 $\times$ , respectively, enhancing the vascular aetiology of the tumour with the atypical endothelial cells staining for this endothelial marker.

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## Conclusions

Primary angiosarcomas of the urinary bladder are rare tumours which tend to affect middle-aged and elderly men who also tend to present with locally advanced disease which exhibit a wide histologic spectrum. Initial reports suggested that the prognosis is poor with fatal outcome. Nevertheless, it would appear that their prognosis may be better than previously thought.

Perhaps if an attempt at cure is feasible, a multimodal therapeutic approach including radical surgery, followed by high-dose adjuvant radiotherapy and combination chemotherapy would appear to be the most appropriate option. Because of the rarity of angiosarcomas of the urinary bladder one cannot be dogmatic about the best combination of chemotherapeutic agents to use.

In view of the rarity of primary angiosarcomas of the urinary bladder, there is no consensus opinion regarding their treatment. There is therefore the need for a multi-centre trial to enable urologists and oncologists to determine the best treatment options associated with improvement of prognosis for these tumours.

## Conflict of Interest

None declared

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