

1 Primary Angiosarcoma of the Prostate Gland: A Review of the Literature

2 Abstract

3 Context

4 Primary angiosarcoma of the prostate (PASOP) is a very rare tumour which most clinicians
5 have not encountered and may be unaware of.

6 Aim

7 To review the literature on PASOP

8 Method

9 Various internet data bases were searched

10 Literature Review

11 Less than 20 cases of PASOP have been reported. PASOP may present in a male child or
12 adult with lower urinary tract symptoms, dysuria, haematuria, pain and constipation. There
13 may be in some cases a history of prior radiotherapy for adenocarcinoma of prostate.
14 Diagnosis is based upon histological examination of prostate biopsy specimens which tend to
15 reveal: proliferative vascular channels that are lined by atypical multi-layered or atypical
16 solid endothelial cells variable pleomorphic tumour cells ranging from spindle cells to
17 large/plump cells; nuclei which are large and pleomorphic and which contain clumped
18 chromatin and prominent nucleoli; mitotic figures of which some may look atypical are
19 frequently seen. PASOPs on immunohistochemical staining tend to stain positively for CD34,
20 Factor 8 (Factor VIII), vimentin. PASOPs on immunohistochemical staining tend to exhibit
21 negative staining for PSA, Keratin and S-100. Surgical resection with surgical margins that
22 are clear of tumour has been shown to be the treatment associated with a chance of long-term
23 survival but a number of reported cases of PASOP at the time of initial diagnosis had
24 presented with metastatic disease or locally advanced disease and curative surgery with clear
25 surgical margins has been impossible. Various adjuvant therapies had been reported but on
26 the whole the prognosis has been poor. There is on the whole no consensus opinion on the
27 best management options for all stages of the disease.

28 Conclusions

29 PASOP is a rare aggressive disease. Clinicians should report cases of PASOP they encounter
30 and should enter them into a multi-centre trial to find the best treatment option. Perhaps if
31 patients who develop relapse disease who had previously undergone radiotherapy for prostate
32 cancer undergo further biopsies of prostate may be new cases of PASOP would be diagnosed
33 in the new biopsy specimens.

34 **Key Words:** Primary Angiosarcoma of the Prostate; CD 34; Factor VIII-related antigen;
35 Vimentin; Radiotherapy; spindle cells; atypical endothelial cells; immunohistochemistry;
36 surgical resection:

37 **Introduction**

38 Primary angiosarcoma of the prostate gland (PASOP) is an extremely rare malignancy which
 39 can afflict children as well as adults. In view of the rarity of PASOP most clinicians would be
 40 unaware of the presentation, the diagnostic features as well as the biological behaviour of the
 41 disease. The question needs to be asked whether or not a number patients globally do develop
 42 angiosarcoma of the prostate but these are not diagnosed because on the whole most patients
 43 who had undergone external beam radiotherapy or brachytherapy for adenocarcinoma of
 44 the prostate gland with curative intent upon relapse of their symptoms do not routinely
 45 undergo repeat prostate biopsies because they are all presumed to have developed relapse of
 46 their adenocarcinomas. Dedifferentiation of toti-potential cells in the prostate gland could
 47 possibly occur following radiotherapy to the prostate gland and the prostate gland could
 48 subsequently develop different types of sarcoma which may occur together with
 49 adenocarcinoma of the prostate gland or perhaps the radiotherapy treatment could possibly
 50 have effectively cured the adenocarcinoma but a de novo sarcoma of the prostate gland alone
 51 may ensue curative treatment of adenocarcinoma of the prostate following radiotherapy of the
 52 prostate. Even though a number of cases of PASOP have been reported which had not been
 53 associated with previous radiotherapy, a handful of cases of PASOP have been reported
 54 associated with previous radiotherapy to the prostate gland for adenocarcinoma. The ensuing
 55 literature review of PASOP is divided into two parts: (A) Overview and (B) Miscellaneous
 56 narrations and discussions from some reported cases of PASOP

57

58 **Methods**

59 Various internet data bases were searched including: Google, Google Scholar, Educus, and
 60 PUB Med. The search words used included: Primary angiosarcoma of the prostate gland,
 61 Angiosarcoma of prostate, prostatic angiosarcoma. Forty-eight references were identified
 62 with information relevant to primary angiosarcoma of the prostate gland which were used for
 63 the literature review.

64

65 **Results / Literature Review**

66 (A) Overview

67 General

68 Primary angiosarcoma of the prostate gland is a very uncommon tumour with less than 20
 69 cases so far reported in the literature. [1]

70 Definition

71 Aetiology / Pathogenesis

72 The exact cause of all the cases of primary angiosarcoma of the prostate cannot be confirmed
 73 for certain. It may be conjectural; however, it could be said that some of the cases of PASOPs
 74 may be de novo carcinomas but others could have resulted from mutation of TP53 tumour
 75 suppressor gene following radiotherapy to the prostate gland for adenocarcinoma of the
 76 prostate gland or radiotherapy as treatment for any other malignancy close to the prostate of
 77 which the prostate gland had been in the radiation field. What is known is that some of the
 78 reported cases of PASOP have been associated with previous radiotherapy treatment for
 79 adenocarcinoma of the prostate gland [2] The criteria to establish a diagnosis of radiotherapy-
 80 induced (radiation-induced) sarcoma, has been stratified by Cahan et al. [2] as follows: [1]

- 81 • The tumour must arise in the area which had been radiated previously.
- 82 • There must be a latent period in years following the radiotherapy preceding the
83 development of the tumour.
- 84 • The diagnosis of sarcoma must be confirmed by means of histological examination.

85

86 Furthermore, in 2012 it had been stated [3] that the association of PASOP with radiotherapy
 87 (radiation therapy), may be weak. With this in mind if there is no direct link of a PASOP with
 88 radiotherapy then such a case PASOP not linked with radiotherapy could be regarded as a de
 89 novo sarcoma unless there is evidence any other direct association with the case of PASOP.

90 Chen et al. [4] in 1979 stated that the direct oncogenic effects of ionizing radiation and the
 91 prolonged stimulation of the cell during the process of tissue repair of damaged tissue which
 92 results from radiation induced ischaemic change have been postulated to play a role in the
 93 development of angiosarcoma. Khaliq et al. [3] had intimated that other different factors had
 94 been linked with the development of angiosarcoma and these include chronic lymph oedema
 95 and exposure to chemicals like arsenic, thorium dioxide and vinyl chloride; however, from
 96 their review of the literature none of the reported cases of PASOP had had an exposure to
 97 chemicals.

98 Cahan et al. [2] had iterated that radiation induced sarcoma could occur in an area which had
 99 been previously radiated within a latent period which is as long as 7 years. Association
 100 angiosarcoma and radiotherapy had previously been reported. In one case Nanus et al. [5] and
 101 in the other case, Navon et al. [6] reported a case of angiosarcoma of the urinary bladder
 102 following therapeutic radiotherapy for adenocarcinoma of the prostate gland.

103 With regard to angiosarcoma of the prostate gland, Khaliq et al. [3] pointed out that their
 104 review of the literature had revealed that out of the ten cases of primary angiosarcoma of the
 105 prostate that had been published in the literature by the time of their publication only 3 of the
 106 patients had previously undergone radiotherapy when the serum PSA levels were within
 107 normal range or PSA was not detectable [7] [8] [9] and based upon this they were of the
 108 opinion that the association between radiotherapy and the development of angiosarcoma of
 109 the prostate was weak.

Other reports of an association between radiotherapy and an increased risk for the development of soft tissue sarcoma following radiotherapy have been reported in association with for: breast cancer [10] [11] [12]

Moon et al. [13] reported an increased risk for the development of a second primary cancer of the urinary bladder, rectum, gastrointestinal tract, brain, lung, lymphoma as well as leukaemia in patients who had been diagnosed as having carcinoma of the prostate gland 5 years pursuant to radiotherapy in comparison to those who did not undergo radiotherapy in a study. Moon et al. [13] also reported that the same study had shown that men who had undergone radiotherapy in the form of isotope or radioactive implants did not have an increased risk for the development of a second primary cancer. Khaliq et al. [3 + 29] observed that in the large cohort study undertaken by Moon et al. [13] no enhanced risk for the development of angiosarcoma of the prostate was reported.

Bagchi Sanjeet [14] reported in 2014, that new research had shown that two novel genes, PTPRB and PLCG1, are associated with the development of angiosarcoma

Epidemiology

Age

- PASOP may affect children and adults

General comments on the epidemiology

Khaliq et al. [3] had stated that: PASOP is very rare and the progression as well as its prognosis on the whole is not clearly understood; A peak incidence of PASOP had been observed to be between 40 years and 50 years with a mean age of 40 years in the literature; one case of PASOP had afflicted a 2 years and 9 months old child; Smith et al. [15] had reported two cases of PASOP and at that time they did find two other cases in the literature from 1889 to 1986 [16] [17]; Chan et al. [18] reported a 35-year-old Chinese man who had PASOP which was said to be the 5th case of PASOP to be reported; Oliva Encina et al. [19] reported a 31-year-old man with PASOP which was considered to be the 6th case of PASOP; Chandran and Wolsh [7] reported a man who was diagnosed as having PASOP, who had ten years earlier undergone radiotherapy as treatment for adenocarcinoma of the prostate gland and this was reported as the 7th reported case of PASOP; Lee et al. [20] reported a 19 year-old man who was diagnosed as having teratoma of the prostate gland which was resistant to chemotherapy and who was subsequently diagnosed as having developed angiosarcoma of the prostate gland, as the 8th reported case of PASOP; Guo et al. [8] reported the 9th case of PASOP in a patient who had undergone radiotherapy 4 years earlier; Khaliq et al. [9] reported a 73-year-old man who had undergone brachytherapy for adenocarcinoma of the prostate gland 8 years preceding his subsequent diagnosis of having angiosarcoma of the prostate gland together with adenocarcinoma of the prostate and the case was reported as the 10th case of PASOP;

The aforementioned few anecdotal case reports would be considered not enough for a full understanding of the epidemiology of PASOP. In view of this there is the need for clinicians

to report new cases of PASOP that are diagnosed so that the biological behaviour and epidemiology of the disease can be fully understood. .

Presentation [7]

Patients with PASOP may present with:

- Lower urinary tract symptoms, urinary frequency, reduced urinary stream
- Dysuria
- Pain
- Haematuria
- Constipation.

Findings on Clinical Examination

Clinical findings in PASOP tend to be non-specific and these may include the following:

- A normal benign feeling prostate, a nodule or nodules on the prostate, enlarged prostate which may or may not extend beyond the prostate.
- There may be blood seen at the external urethral meatus in cases of PASOP associated with haematuria
- If the patient has retention of urine then the urinary bladder would be palpable or the supra-pubic region may be dull on percussion.

Laboratory Investigations

Urine analysis, microscopy, culture and sensitivity

- Urinalysis, urine microscopy, urine culture and sensitivity are part of the general assessment of the patient to find out whether or not there is any urinary tract infection which could be treated prior to biopsy or treatment of PASOP

Haematological Investigations

- Full blood count and coagulation screen are non-specific tests that are carried out in the general assessment of the patient but usually there would be no specific abnormality related to the PASOP. Nevertheless, when a patient develops massive bleeding following biopsy of the prostate or trans-urethral resection of the prostate the patient could develop anaemia or even eventual evidence of disseminated intravascular coagulopathy.

Biochemistry Investigations

181 • Serum urea, renal function tests, liver function tests and bone profile are
 182 investigations that form part of the general assessment of the patient and these may be
 183 normal or abnormal depending upon whether the patient has retention or urine or
 184 metastatic disease.

185 • Serum prostate specific antigen and serum prostate-specific acid phosphatase would
 186 tend to be normal but in situations when there is mixed tumour of PASOP associated
 187 with adenocarcinoma of the prostate gland then the serum PSA level may be raised.

188 Radiological Investigations

189 Ultrasound scan

190 • Ultrasound scan of abdomen and pelvis findings may be variable depending upon the
 191 state and stage of the disease and this may show normal upper renal tracts and normal
 192 urinary bladder, or unilateral/bilateral hydronephrosis, trabeculated urinary bladder, a
 193 lesion/mass in the prostate which may be localized to one lobe or both lobes or which
 194 may extend and invade the bladder or the seminal vesicle or extend beyond the
 195 capsule of the prostate towards the rectum or pelvic side wall.

196 • Trans-rectal ultra-sound scan of prostate can be done to assess the prostatic lesion and
 197 as a guide to taking biopsies of the prostate for histological examination to establish a
 198 diagnosis.

199 Computed tomography (CT) scan

200 • CT scan of abdomen, pelvis and thorax tends to be done as part of full assessment of
 201 the extent of the tumour.

202 Magnetic Resonance Imaging (MRI) Scan

203 • MRI scan of pelvis, abdomen and thorax is a useful radiological investigation to
 204 assess the prostatic lesion and the define the extent of the tumour

205 Isotope Bone Scan

206 • Isotope bone scan is a useful investigation to determine whether or not there is
 207 metastasis in the bone

208 Macroscopic Features

209 • Gross examination of the prostate gland in PASOPs may reveal a tan-brown prostatic
 210 tumour [1] [7] with extensive necrosis and perhaps bleeding may be seen from the
 211 tumour

212 Microscopic Features

213 Microscopic examination of PASOPs would tend to show the following (see figures 1, 2, and
 214 3 for example: [1] [7] chandan and wolsh & pathology outlines.com]

- 215 • Proliferative vascular channels that are lined by atypical multi-layered or atypical
- 216 solid endothelial cells
- 217 • Variable pleomorphic tumour cells ranging from spindle cells to large/plump cells
- 218 • Nuclei which are large and pleomorphic and which contain clumped chromatin and
- 219 prominent nucleoli
- 220 • Mitotic figures of which some may look atypical are frequently seen.

221 Immunohistochemistry Characteristics

222 Positive Immunohistochemistry

223 PASOPs on immunohistochemical staining tend to stain positively for the following

- 224 • CD34
- 225 • Factor 8 (Factor VIII)
- 226 • Vimentin

227 Negative Immunohistochemistry

228 PASOPs on immunohistochemical staining tend to exhibit negative staining for the
229 following:

- 230 • PSA
- 231 • Keratin
- 232 • S-100
- 233

234 Differential Diagnosis

235 Other forms of carcinomas of the prostate gland that need to be differentiated from PASOP
236 include: carcinosarcomas, osteosarcomas, chondrosarcomas, leiomyosarcomas,
237 rhabdomyosarcomas, synovial-cell sarcomas, adenocarcinomas admixed with other types of
238 sarcomas, lymphoepithelioma-like carcinoma.

239 Treatment

240 General Comments on treatment

241 In view of the fact that very few cases of PASOP have been reported and the fact that
242 globally no clinician has the experience of managing many cases of PASOP, there is no
243 consensus opinion of the management of PASOP. Important facts that need to be taken into
244 consideration include the size of the prostatic tumour, whether the tumour is localized and
245 can be surgically excised completely by means of radical cystoprostatectomy or radical
246 prostatectomy to be able to achieve complete tumour clearance at the surgical margins,
247 whether or not there any lymph nodes involved by the tumour or there are metastases. With

regard to the first ten cases of PASOP that had been reported, six patients had undergone radical cystoprostatectomy and two patients had undergone sub-total resections of the prostate gland, one patient died shortly after his admission to hospital, and one patient was lost to follow-up. With regard to the six patients reviewed by Khaliq et al. [3] who had undergone radical cystoprostatectomy surgical margin clear of tumour was achieved in only one patient. Three of the patients who had undergone cystoprostatectomy had also received adjuvant chemotherapy which had comprised of doxorubicin in one of the cases, experimental thalidomide in another patient, and ifosfamide and doxorubicin in the third patient. Khaliq et al. [3] noted that none of the patients had been treated by means of radiotherapy presumably because of the notion that radiotherapy to adenocarcinoma may induce angiosarcoma or other types of prostatic tumours. One patient who had undergone trans-urethral resection of prostate [7] and removal of blood clots from the urinary bladder and who developed severe haematuria post operatively requiring transfusion with several units of blood. He developed disseminated intravascular coagulopathy and died. Histological examination of the resected specimen was reported as showing angiosarcoma of the prostate gland. Lessons learnt from this case is the fact that angiosarcoma is a vascular lesion which can bleed severely in view of this necessary precautions would have to be taken by the clinician to avoid/minimise or promptly treat such bleedings in the form of pre- or post-operative selective angiography and selective/super-selective embolization of the bleeding artery to the prostatic tumour. In the aforementioned case the diagnosis was known perhaps after the patient had died. Even though some people are of the view that the evidence for radiotherapy induced angiosarcoma of the prostate is weak, it would be argued since some cases of angiosarcoma following radiotherapy have been reported one should always consider the possibility of angiosarcoma of the prostate developing many years after undergoing radiotherapy for adenocarcinoma of prostate. If a patient who had undergone radiotherapy for carcinoma of the prostate gland subsequently presents with lower urinary tract symptoms or haematuria, a digital rectal examination should be undertaken irrespective of the level of serum PSA and if a nodule or mass is palpable on the prostate then ultrasound-guided biopsy should be undertaken of the mass. If the histology of the biopsy specimen confirms angiosarcoma of the prostate then it would be recommended that the interventional radiologist should be involved in a multi-disciplinary approach plan of management so that a possible pre-operative or post-operative embolization of the artery supplying the tumour is undertaken to avoid or minimize excessive exsanguinating bleeding.

Treatment of localized disease

Considering the fact that very few cases of PASOP have been reported one cannot be absolutely sure what the best treatment option for this aggressive disease should be. Perhaps lessons learnt from the management of angiosarcomas could be used as a guide for the management of angiosarcoma of the prostate gland. It would appear that radical surgery of with complete resection with tumour margins that are clear of tumour should be the treatment of choice but this can be hampered by the size of the tumour, invasion of other tissues by the tumour, as well as the relationship of the tumour to nearby critical organs and these factors have tended to be associated with prognosis. [21] [22] [23] With regard to a number of patients who had developed recurrent angiosarcoma, Lahat et al. [24] had observed that

patients who undergone surgical excision of the tumour for localized disease with histopathological evidence of complete resection of tumour and absence of tumour at the surgical resection margins had improved survival in comparison with those patients who had tumour at the resection margins. On the whole it is usually the aim of every surgeon to achieve complete resection of tumour in any type of malignancy as a treatment of curative intent if the tumour is resectable. Khaliq et al. [3] had stated that on the whole adjuvant radiotherapy had been recommended for the treatment of sarcomas with the aim of reducing or preventing local recurrence in cases of sarcoma but they pointed out that randomized controlled had not been undertaken related to the use of adjuvant radiotherapy in sarcomas. However, Khaliq et al. [3] pointed out that Pawlik et al. [23] had reported an overall survival in patients who had had adjuvant radiotherapy. Controversies exist regarding the place of the use of adjuvant chemotherapy in the treatment of sarcomas with some reports documenting improved survival [25] [26] [27] and others not finding any improved survival with adjuvant chemotherapy. [28]

Treatment of metastatic disease

In view of the very few cases of PASOP that have been reported there is no consensus opinion on the best treatment option or useful options of its treatment. It would appear as if there is no consensus opinion in the choice of management regimes for treating angiosarcomas afflicting other organs too. Khaliq et al. [9] stated that on the whole cytotoxic chemotherapy with the use of anthracyclines, ifosfamide, and taxanes have been the primary treatment of choice for metastatic angiosarcomas on the whole. Mocellin et al. [29] had stated that generally the use of combination chemotherapy in the treatment of metastatic angiosarcoma had been associated with increased incidence of toxicities and its use had failed to provide improvement in the overall survival of patients with angiosarcoma. Generally the use of various combination chemotherapeutic regimens had been associated with various response rates. [30] [31] [32]. Some of the other therapeutic agents, that had been used include: VEGFA, monoclonal antibody, bevacizumab [33], interferon- α , [34], [35] interferon- α in combination with doxorubicin, [36] interleukin-2 has been used in as a single agent as well as in combination with chemotherapy or with radiotherapy, [37]. Khaliq et al. [9] had stated that at the moment, interleukin-2 and interferon- α , are only being used in clinical trials and on the whole their use outside clinical trials. The aforementioned information would strongly confirm that there is a great need for all cases of angiosarcoma of the prostate gland to be reported and entered into a global multi-centre trial in order to find the best treatment option for the disease and to ascertain their biological behaviour.

Outcome

In view of the fact that very few cases of PASOP have so far been reported in the literature it would be argued that the true biological behaviour of PASOP would not be known. Nevertheless, what is known is that patients six (60%) out of the first ten reported patients, who were diagnosed as having PASOP had died within 9 months of the diagnosis of their tumours and three of the patients were free of their disease (without residual local disease or metastasis) over a period of 16 months, 24 months and 36 months respectively but one of the patients was lost to follow-up. The aforementioned outcome would indicate that perhaps mortality in cases of PASOP should be expected to be high unless a treatment option is found that would improve the prognosis. Whether or not the biological behaviour of PASOP would be similar to the prognosis associated with treatment of angiosarcomas of other sites of the

body would not be known at present. However, it has been reported that the five-year survival for soft-tissue sarcomas has ranged between 50% and 60% [29] and that the five-year survival for angiosarcomas at any site was 35%. [21] [22] [38] Young et al. [28] had stated that suspected factors for poor prognostication for other types of soft-tissue sarcomas include: tumour size greater than 5 cm, the histological grade of the tumour, advanced age, location of angiosarcomas in retroperitoneal locations, presence of metastases, and poor patient performance.

(B) Miscellaneous narrations and discussions from some reported cases (see table 1 for reported cases)

Chandan and Wolsh [7] reported a 77-year-old man who had presented in 2002 with visible haematuria, urinary frequency, dysuria, and bladder spasms. He was asymptomatic otherwise. Ten years earlier in 1992 he had undergone external beam radiotherapy for stage B, Gleason 7 adenocarcinoma of the prostate gland and since then he had been having follow-ups for his previously treated adenocarcinoma of the prostate gland. His latest serum PSA in 2002 was 0.0023 ng / ml (normal range 0-0.04 ng / ml). His clinical examination on the whole was normal. He had a CT scan of abdomen, pelvis, and thorax which did show a large mass arising from the prostate gland. There was no evidence of metastasis in his chest X-ray and CT scan of the thorax. He underwent urethrocystoscopy which revealed a tri-lobar prostatic enlargement with irregular prostatic enlargement encroaching upon the prostatic urethra. There was also blood clot in his urinary bladder. He underwent trans-urethral resection which removed the protruding prostatic tissue in his prostatic urethra and prostatic tissue in the base of the urinary bladder. The specimen was sent for histological examination. He continued to have visible haematuria post-operatively and was given several units of blood transfusion. He developed disseminated intravascular coagulopathy and died 4 days after his surgical operation. Gross examination of the specimen of the resected prostate, did reveal a 15 grams of tan-brown soft tissue, which had been mixed with blood clot. Histological examination showed that less than 10% of the specimen was had viable tissue and the remaining approximately more than 90 percent of the tissue, was necrotic. The viable tissue was found to comprise of vascular channels that had been lined by atypical endothelial cells which had been encompassed by spindle-shaped cells. The tumour cells were adjudged to be pleomorphic and they had varied from elongated and spindle-shaped cells to large and plump cells. The nuclei were observed to be large and pleomorphic and they had clumped chromatin and the nucleoli were prominent. Mitotic figures were frequently observed and some of the mitotic figures looked atypical (see figure 1). The histological examination also revealed that the area of the prostatic urethra did show prominent von Brunn nests without showing any evidence of atypia. Immunohistochemical staining of the specimen had revealed positive staining for factor VIII-related antigen (see figure 2), CD 34 (see figure 3), and vimentin in the tumour cells. Based upon the aforementioned findings a diagnosis of angiosarcoma of the prostate gland was made. Chandan and Wolsh [7] stated the following:

- In order to establish a diagnosis of radiotherapy-induced angiosarcoma, Cahan et al. [2] had suggested the ensuing criteria: (a) the sarcoma should arise in an area which had been previously been subjected to radiotherapy treatment; (b) a latent

period in years must exist between the time of radiotherapy treatment and the development of the sarcoma; (c) the sarcoma must be diagnosed by means of histological examination. Based upon the Cahan et al. [2] criteria their patient had satisfied the criteria for the diagnosis of radiotherapy-induced angiosarcoma of the prostate gland.

- Kim et al. [12] had reviewed 66 reported cases of angiosarcoma and reported that the commonest primary cancer for which the radiotherapy treatment was given was carcinoma of the breast which constituted 44% of the cases; and gynaecological cancer constituted 21% of the cases for which radiotherapy was given. Eighty-five percent of the radiotherapy-induced angiosarcoma had developed in cutaneous areas; the median age at diagnosis of the angiosarcoma was 65 years; the median latent period from the time of the previous radiotherapy and development of angiosarcoma was 96 months; the median survival period from the time of the diagnosis of the angiosarcoma was 12 months.
- The causal relationship between radiotherapy and the development of angiosarcoma had been discussed previously; nevertheless, Cafiero et al. [39] had indicated that there is little doubt that bona fide post-radiotherapy-induced angiosarcoma does occur. Chen et al. [4] had intimated that apart from the direct oncogenic effect of direct irradiation, prolonged cellular stimulation during repair of tissue damage that has emanated from radiotherapy induced ischaemic change may have a role to play in the development of angiosarcoma.
- Their observations from the 6 previously reported cases of post-irradiation-induced angiosarcoma of the prostate gland were as follows: At the time of diagnosis of angiosarcoma of the prostate, the patients' ages had ranged between 2 years and 65 years and the mean age was 34.5 years; one case had involved a child who was aged 2 years and 9 months; the presenting symptoms of the patients had included dysuria and haematuria; with regard to outcome, 3 patients had died of the angiosarcoma within the first 6 months of the initial diagnosis, 2 patients were free of angiosarcoma for a period of 24 months and 36 months, and one patient did not have a follow-up.
- Navon et al. [6] had reported 1 case of post-radiotherapy-induced angiosarcoma of the urinary bladder which had developed 13 years after the patient had undergone radiotherapy for adenocarcinoma of the prostate gland; they would speculate that as radiotherapy for prostate cancer improves survival, the incidence of post-radiotherapy should be expected to increase; Mart et al. [38] had estimated the risk for the development of post-radiotherapy-induced sarcoma after a long period of follow-up to be from 0.03% to 0.8%; literature review which had compared the mortality risks of chemotherapy, general surgery and anaesthesia had indicated that the risk of post radiotherapy sarcoma was not worse and that concerns related to the possibility of the development of post-radiotherapy sarcoma should not be an influential factor in taking management decisions; pathologists would need to be

424 aware of the possibility of post-radiotherapy angiosarcoma in patients who present
425 with haematuria and / or dysuria when they had previously undergone
426 radiotherapy.

427 Khaliq et al. [9] in 2012 reported a case of angiosarcoma of the prostate which
428 was associated with adenocarcinoma of the prostate and they stated that from
429 their search of the literature, their case was the 10th case of angiosarcoma to be
430 reported in the literature because their literature search had revealed 9
431 previously reported cases. [9]

432
433 Smith et al. [15] in 1986 reported 2 cases of angiosarcoma of the prostate
434 gland in patients who were aged 42 years and 60 years. Immunohistochemical
435 staining of the tumours for factor VIII associated antigen was positive in the
436 two cases and this in the opinion of the authors was very useful with regard to
437 the confirmation of the diagnosis in one case which was otherwise a poorly
438 differentiated tumour. One of the patients who underwent surgical excision
439 was alive without any evidence of recurrent tumour 2 years after he had
440 undergone surgical excision of his tumour. On the other hand, the other patient
441 who had presented with unresectable tumour died 6 months after he had
442 presented. Smith et al. [15] stated that even though angiosarcoma constitutes
443 less than 2 percent of sarcomas of the prostate gland it should be considered in
444 the differential diagnosis of poorly differentiated sarcomas, especially those
445 that occur in adults. [15]

446
447
448 Campschoer et al. [40] reported a 69-year-old man who presented with
449 voiding symptoms which had culminated in retention of urine. Eight years
450 prior to his admission, he had been diagnosed with a Gleason 6
451 adenocarcinoma of prostate and his initial serum prostate-specific antigen
452 (PSA) level was 6.6 ng / ml. He underwent brachytherapy and his most recent
453 serum PSA about 8 years pursuant to his brachytherapy was 0.11 ng / ml. He
454 underwent cystoscopy and trans-urethral resection of prostate on two
455 occasions as well as trans-rectal ultrasound guided biopsies of the prostate of a
456 cystic mass arising from the prostate. Histological examination showed
457 necrosis and extensive inflammation in the first resected prostatic tissue and
458 lymphoid tissue and necrosis in the biopsy specimen. Histological examination
459 of the second resected prostatic specimen revealed features consistent with
460 angiosarcoma of the prostate with evidence of inflammation and necrosis.
461 Immunohistochemical staining of the tumour showed positive staining for
462 CD31, CD34, vimentin, and factor VIII but negative staining for PSA. His
463 pubic bone was involved by the tumour. He was adjudged to be unfit to
464 undergo surgery or chemotherapy. He died within 4 months of his diagnosis
465

466 Campschoer et al. [40] searched for literature on angiosarcoma of the prostate
467 gland using various internet data bases. They included their case of PASOP in
468 the review. Campschoer et al. [40] identified 13 cases of angiosarcoma of the
469 prostate gland and of the 13 cases they had included in their analysis, they had
470 found that the earliest six publications had lacked essential data in their
471 opinion. They stated the following:

- Out of the 13 patients, four patients did have a history of having undergone radiotherapy treatment previously.
- With regard to five of the patients their treatment had consisted of radical surgery with or without chemotherapy. With regard to eight of the cases curative treatment was either not reported or not possible.
- The mean follow-up was only for a period of one year.
- With regard to outcome, four of the 13 patients had died within one year of their diagnosis, irrespective of the choice of treatment. One patient, who had undergone a combination of radical surgery and adjuvant chemotherapy, was still alive 36 months pursuant to his treatment.

Campschroer et al. [40] concluded that their patient was the first case of angiosarcoma of the prostate gland following primary brachytherapy to be reported; angiosarcoma may develop more often in the future due to the widespread use of brachytherapy and radiotherapy of the prostate gland; the current guidelines on the treatment of angiosarcoma recommend radical surgery in the case of local disease as the primary treatment of choice.

Humphrey, [41] reported a 67-year-old man who presented with urinary tract obstructive symptoms 7 years after he had undergone radiotherapy for adenocarcinoma of the prostate gland. He underwent trans-urethral resection of prostate (TURP) which was followed by pelvic exenteration. Macroscopic examination of the specimen revealed that the prostate gland had been replaced by a 7.5 cm haemorrhagic mass which had extended into the urinary bladder. Histological examination of the specimen did show a neoplastic spindle proliferation which had formed irregular vascular channels that had dissected through the stroma of the prostate gland and the urinary bladder. Other areas of the tumour were noted to be more solid and admixed with the vascular spaces. The channels were observed to be lined by neoplastic endothelial cells which had displayed nuclear atypia. Immunohistochemical staining of the tumour had showed that the tumour cells were positively stained for CD31, CD34, and Factor VIII-related antigen. Immunohistochemistry of the tumour had also shown negative staining for pan-cytokeratin, prostate specific antigen and prostate specific acid phosphatase which confirmed that there was no residual adenocarcinoma of the prostate and that the endothelial spindle cell endothelial tumour was indeed angiosarcoma of the prostate gland. Humphrey [41] stated the following:

- Exposure to radiation had been linked to sarcomas of the prostate but upon taking into consideration the frequency of radiotherapy, these cases of post-irradiation sarcomas of the prostate are rare, with only few cases reported [42]

- A post-irradiation (post-radiotherapy) sarcoma may be designated as such if the sarcoma develops in the irradiated field, and there is histological establishment of the diagnosis of sarcoma, a latency of at least 3 years between the radiotherapy (irradiation) and the appearance of the tumour, and documentation that the sarcoma had occurred in tissue which was normal before the radiotherapy. Majority of cases of post-irradiation sarcoma of the prostate gland that had been reported in the literature were diagnosed after radiotherapy for carcinoma of the prostate gland and in their opinion should not formally be considered post-irradiation sarcoma in view of the fact that the sarcoma developed in prostatic tissue that was not normal, having been previously involved with adenocarcinoma.

It would be argued that the suggestion of Humphrey [41] that the terminology of post-irradiation sarcoma of the prostate gland should not be used because the prostate gland which had been irradiated had been afflicted by disease prior to the irradiation was not a normal prostate is not absolutely correct. The reason is that when biopsies of the prostate gland that had been afflicted by adenocarcinoma of the prostate gland are taken histological examination tends to show various percentage areas of the prostate that have tumour tissue and areas of the prostate that are normal. There is a likelihood that the sarcomas had developed from cells in the prostate gland that were normal. It is only if the sarcoma is shown to have arisen from a cell that had been afflicted by adenocarcinoma that the suggestion of Humphrey [41] would be correct. What is important in cases of angiosarcomas of the prostate gland or other types of sarcoma of the prostate gland is for clinicians to obtain permission from their patients to undertake genetic studies to show whether there had been mutation of TP53 tumour suppressor gene or any other gene that could be attributed to the radiotherapy and to search for treatment modalities that would improve prognosis of PASOP. Considering the fact that biopsies of the prostate gland or trans-urethral resection of the prostate gland afflicted by PASOP may be associated with excessive bleeding the role of embolization to stop post biopsy bleeding and post trans-urethral resection of prostate excessive bleeding would need to be encouraged. Furthermore, considering the fact that some patients with PASOP may have large tumours which may prove difficult to surgically excise completely with clear margin, there is the need to develop treatment strategies on global study trials with the aim of reducing the mass of PASOP to make it possible to completely achieve complete local resection. With regard to the aforementioned aim, the role of the newly developing nanotechnology with particular reference to electroporation would need to be considered. It

may be that by subjecting a patient with a histologically proven PASOP to electroporation of the prostatic disease the tumour may significantly reduce in size or the tumour may be successfully treated without the need to undergo any surgical operation. This assumption is only conjectural because to the knowledge of the author electroporation has never been used as a treatment option in the treatment of PASOP

Gupta et al. [43] reported a case of angiosarcoma of the prostate gland in a 71-year-old man who had presented with lower urinary tract symptoms and visible haematuria 5 years after he had been treated by means of brachytherapy for adenocarcinoma of the prostate gland. Five years prior to his presentation he had a routine serum PSA which was recorded as 4.0 ng / ml. He had biopsy of prostate and histological examination of the specimen had revealed Gleason 3 + 3 = 6 adenocarcinoma of the prostate for which he was treated by means of brachytherapy and following this his serum PSA became undetectable. During his recent admission, his rectal examination revealed an enlarged prostate. He had a CT urogram which had revealed a 6.1 cm x 5.3 cm partially necrotic mass which had involved the right postero-lateral aspect of the urinary bladder and this had extended into the perivesical and right iliac lymph nodes. He had urodynamic assessment which had demonstrated bladder outflow obstruction. He had cystoscopy and biopsy of the mass which had involved the bladder neck and the prostatic urethra and histological examination of this had confirmed angiosarcoma of the prostate. The histological examination of the specimen showed benign duct epithelium and undifferentiated spindled prostatic angiosarcoma and immunohistochemistry of the tumour showed strong and diffuse staining for FLI-1, CD31, CD117, it also showed negative staining for CD34, various keratins (OSCAR, keratin AE1/AE3, CAM 5.2, 7, 20, and 34betaE12), PSA, prostatic acid phosphatase, actin, desmin, and thyroid transcription factor. He underwent radical cystoprostatectomy, pelvic lymph adenectomy and construction of ileal loop urinary diversion. Histological examination of the specimen showed grade 4/4 angiosarcoma with epithelioid features and that the tumour had involved the anterior and right lateral wall and trigone of the urinary bladder, the right seminal vesicle and the entire prostate. Metastatic angiosarcoma had also involved the obturator and hypogastric lymph nodes. He had PET scan which did not show any evidence of distant metastasis. He had received 3 different chemotherapy regimens but there continued to be progression of the disease in the pelvic lymph nodes. (He had paraclitaxel in the first instance (3 cycles), doxorubicin in the second instance (3 cycles), and ifosfamide in the third instance. The patient was alive at the time of the report of his case.

575 Gupta et al. [43] stated the following:

- 576 • Even though adenocarcinoma of the prostate is very common in men only a handful
577 of cases of angiosarcoma of the prostate have been reported in the literature.
- 578 • Prior radiotherapy for adenocarcinoma of the prostate gland had been postulated to be
579 a risk factor for angiosarcoma.
- 580 • In view of the increasing practice of screening for prostate cancer and the use of
581 radiotherapy in the management of adenocarcinoma of the prostate there is the
582 likelihood that this would lead to the development of more cases of angiosarcoma of
583 the prostate gland.
- 584 • Diagnosis of angiosarcoma of the prostate gland is made by tissue sampling
585 (histological examination of tissues obtained from the prostate gland).
- 586 • The optimal management of these aggressive angiosarcomas of the prostate remains
587 to be defined and the outcomes tend to be poor with a-high 1-year mortality.
- 588 • Primary care physicians and urologists should be aware of this rare entity of primary
589 angiosarcoma of the prostate gland and refer these patients to Specialist Centers
590 where cases of PASOP can be managed by a multi-disciplinary team.

591 The etiology / pathogenesis of PASOP may not be completely understood but
592 it is likely that there are multi-factorial elements to the development of
593 PASOP. It is likely that some PASOPS develop and other PASOPS may
594 develop through mutation of TP53 tumour suppressor gene or other genes.
595 Whether radiotherapy does induce genetic changes including mutations and
596 deletions pursuant to treatment for prostate cancer would need to be proven
597 through a global multi-center study. Nevertheless, the postulate that there is
598 the likelihood that radiotherapy induced angiosarcoma of the prostate gland
599 does occur cannot be discounted taking into consideration the fact that in 6
600 cases out of 14 reported cases of PASOP reported a clear history of prior
601 radiotherapy to the prostate gland had been documented and the latency period
602 in each case has been more than 3 years (less than 20 [about 17] cases of
603 PASOP have so far been reported but detailed information on four more cases
604 was not available see table 1).

605
606
607 Scharpira et al. [44] in 1963 reported a case of angiosarcoma of the prostate
608 gland but the details are not available. Wick et al. [45] in 1989, reported two
609 patients, one aged 63 years and the other 69 years. One of the patients had
610 osseous metastasis which was treated by means of radiotherapy and
611 diethylstilbesterol but the treatment was not successful. The second patient was

free of disease 15 months after he had undergone radical prostatectomy. Wick et al. [45] also reported that both tumours did contain a mixture of carcinoma and sarcoma and that the first patient's tumour had displayed foci of chondrosarcoma, osteosarcoma, and leiomyosarcoma but the second patient's tumour on the other hand, exhibited areas of chondrosarcoma, osteosarcoma, rhabdomyosarcoma, and angiosarcoma. The tumours on immunohistochemical staining showed positive staining for vimentin, S-100 protein, desmin, actin, myoglobin, Ulex europaeus 1 agglutinin. Whilst the sarcomatous elements were negatively stained for prostate-specific antigen, epithelial membrane antigen, and cytokeratin, the carcinomatous elements of the tumours were positively stained for prostate-specific antigen, epithelial membrane antigen and cytokeratin. Considering the fact that the second case of carcinosarcoma which contained angiosarcoma also contained other types of sarcoma as well as carcinoma components in the tumour one cannot predict which element of the mixed tumour would be most predominant in the determination of the outcome of the patient.

Russo et al. [46] reported 1 case of angiosarcoma of the prostate gland out of 43 adult soft tissue sarcomas that had been admitted to the Memorial Sloan Kettering Cancer Center (MSKCC) between July 1982 and December 1989. The details of the cases are not separately available to the author.

Luque Barona et al. [47] reported 2 patients who were aged 71 years and 78 years respectively who were diagnosed as having carcinosarcoma of the prostate gland. They reported that the primary tumour of the prostate gland in the first case was composed of adenocarcinoma which was admixed with a neoplastic mesenchymal component which had displayed foci of chondrosarcoma, rhabdomyosarcoma, and angiosarcoma. With regard to the second case, the adenocarcinoma was admixed with spindle cell carcinoma and chondrosarcoma. Both of the patients died of their disease at 3 months and 9 months respectively after surgery. Details of the two cases reported are not available to the author therefore it is not clear whether any of the patients had previously had radiotherapy or not.

Boucher et al. [48] reported the cytological features of 15 cases of angiosarcomas from various sites and among these cases, one case (a 79-year-old man) had represented a cervical lymph node metastasis from a primary prostatic epithelioid angiosarcoma. Histological examination of the primary prostatic tumour showed low-grade epithelioid angiosarcoma of the prostate and histological examination of the cervical lymph node also showed low-grade epithelioid angiosarcoma. Immunohistochemical studies showed negative staining for prostate-specific acid phosphatase (PSAP), prostate specific antigen (PSA) and cytokeratin; and factor VIII-related antigen was positive as well as CD31 was positive in the in the primary tumour. Details of the case including exposure to radiotherapy are not available to the author.

Conclusions

Primary angiosarcoma of the prostate gland (PASOP) is a rare aggressive tumour which can afflict children and adults. Less than 20 cases of PASOP

have so far been reported. It has been postulated that prior radiotherapy for adenocarcinoma of the prostate gland is a risk factor for the development of PASOP. In view of the few reported cases of PASOP the true biological behavior of the tumour may not be well known and it would appear that there is no consensus opinion on the best treatment options that would improve the outcome of PASOP. In view of the increased practice of screening for adenocarcinoma of prostate and the increasing use of radiotherapy as treatment of curative intent for adenocarcinoma of the prostate gland there is the likelihood that there would in the future be an increase in the number of reported cases of PASOP provided clinicians repeat biopsies of prostate glands in patients' whose diseases have relapsed after radiotherapy of their prostate glands. A global multi-Centre-trial is needed to find treatment options that would improve the prognosis of PASOP

Consent

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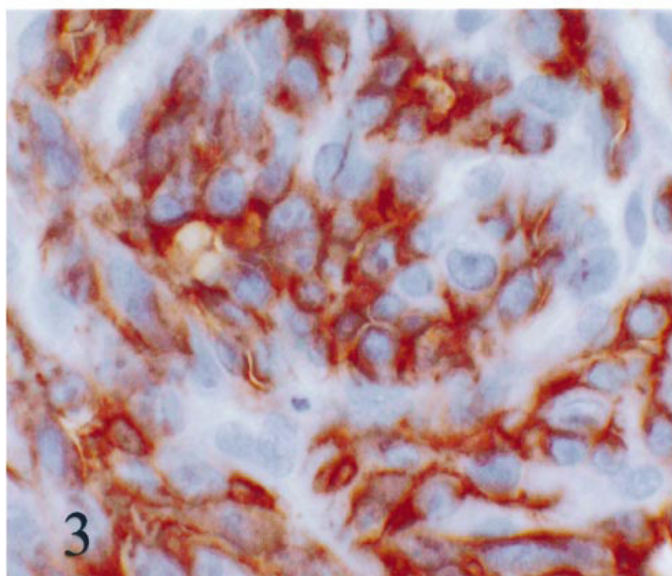
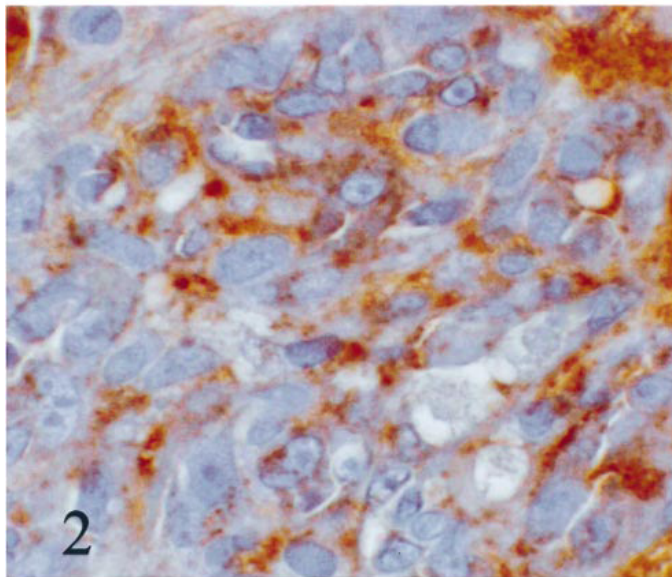
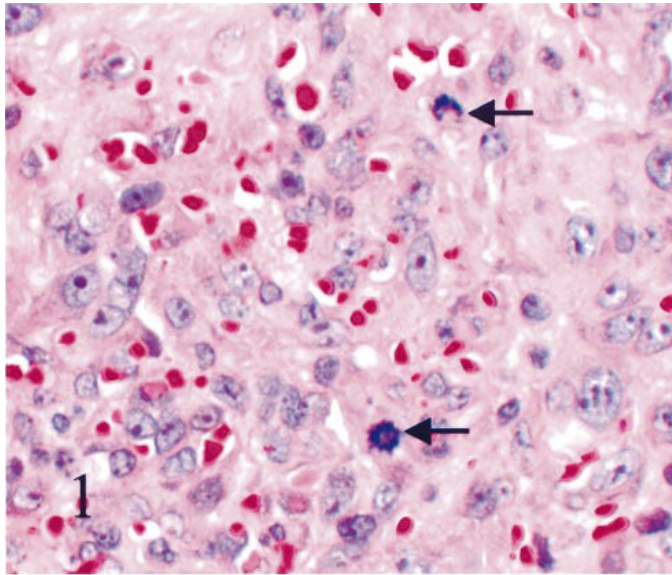
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Figures 1, 2, and 3:

Figure 1: The tumor consisted of pleomorphic cells and large nuclei with clumped chromatin and prominent nucleoli, Mitoses are easily seen (arrows). Vascular channels lined by atypical endothelial cells are present within the tumor (hematoxylin-eosin, original magnification, X 400).

Figures 2 and 3: Tumor cells show positive staining for factor VIII-related antigen (Figure 2) and CD 34 (Figure 3) (immunohistochemistry original magnification, X 400).

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902 Table 1: A list of reported cases of primary angiosarcoma of the prostate gland

903

Authors/Reference/Year	Age/Presentation	Metastasis/No metastasis	Exposure to cancer radiotherapy or not	Histopathology of tumour	Treatment	Outcome	
Botesco et al. [16] 1902	2 years 9 months; Dysuria & constipation	No metastasis	No	Many neoplastic blood vessels, degenerative connective tissue, lymphocytic infiltrates	Died 1 day after admission	Died 1 day after admission	
Salleras and Vilar [17] 1924	32 years; dysuria, constipation & haematuria	No metastasis	No	Many vascular spaces associated with round or spindle,	Was lost to follow-up but was terminally ill	Was lost to follow-up	

				at times multi nucle ated cells			
Smith et al. [15] 1986	60 years; reduced stream of urine, urinary frequency	Local lymph node tumour involvement	No	Sheet s of solid or round pleo morp hic cells whic h had abun dant cytop lasm; enlar ged hyper chro matic pleo morp hic nucle i; the tumo ur cells were lining slit- like space s whic h conta	Radical cysto prost atecto my & partia l resect ion of pubic bone, ureter o- ileal diver sion plus pelvi c lymp h adene ctom y. The tumo ur had exten ded to the pelvi c wall margi n & was	He died at 6 mont hs	

				ined blood with prominent tufts; Immunohistochemistry was positive for factor VIII.	not resectable; 12 out of 22 lymph nodes contained tumour deposits, Adjuvant chemotherapy could not be given because of the patient's poor functional status		
	42 years; Pain	No metastasis	No	Pleomorphic elongated	He underwent radical	Alive & free of disease at	

			spindled cells; the nuclei of the tumour had varied from small and pyknotic to large and vacuolated and with clumped chromatin which contained one or more nucleoli; there were rare vascular structures	cystoprostatic myoepithelial lymphadenectomy ureteric diversion. The resection of the tumour was complete with the surgical resection margins clear of tumour. He also received adjuvant chemotherapy	24 months follow-up	
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				ures which had been lined with magli bnant cells; immu nohis toche mical staini ng of the tumo ur show ed positi ve staini ng for Facto r VIII. The histo patho logy was adjud ged to be consi stent with poorl y differ entiat ed	other apy 2 mont hs after his opera tion with doxor ubici n 70 mg/m² which was follo wed by 3-week interv al with 75 mg /m² for a total of 6 cours es		
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				sarcoma with angiosarcoma with features of angiosarcoma.			
Chan et al. [18] 1990	35 years; pain, haematuria, urinary frequency	Metastases in lung, spleen, liver & mesentery	No	Nodules of cellular & vascular tumour tissue in the prostate gland; the vascular areas were lined with neoplastic cells which were spindle shaped and which	He developed massive haematuria after prostate biopsy which required CT guided selective angiography and embolization. He died as a seque	He died after 5 weeks	

				h had frequent mitotic figures; the tumours exhibited positive immunohistochemical staining for factor VIII and vimentin.	l of disseminated intravascular coagulopathy (DIC) 4 days later		
Oliva Enchina [19] 2001	31 years; LUTS, urinary urgency, dysuria, incomplete emptying of bladder and decreased libido	No metastasis	Epithelial angiosarcoma which had infiltrated the urinary bladder and prostate gland. The	Radical prostatectomy with partial resection of the bladder neck and ileo-obturator lymph	He was alive and free of disease at 36 months follow-up.		

			tumour on immunohistochemical staining stained positively for factor VIII and CD21	haden ectomy; the margins were not clean (not free of tumour). He received six cycles of adjuvant chemotherapy with ifosfamide and adriamycin as well as radiotherapy			
Chandan and Wolsh [7] 2003	77 years; visible haematuria, urinary frequency, dysuria, and	No metastasis	History of adenocarcinoma of	proliferating vascular channel	Trans-urethral resection of	He died at 4 days	

	spasm		prostate, Gleason 7 which was treated by means of external beam radiotherapy 10 years preceding his presentation. His presenting serum PSA at the time of diagnosis of PAS OP was 0.0023 ng/ml (within normal	elements which were lined by atypical endometrial cells that were surrounded by spindle-shaped cells. The tumour cells were noted to be pleomorphic with clumped chromatin and prominent nucleoli. Immunohis	prostate (TURP) and post-operatively developed massive bleeding/hæmaturia and died 4 days later.		
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			al range)	toche mistr y of the tumo ur was positi ve for factor VIII, CD34 and vime ntin.			
Lee et al. [20] 2006	19 years; dysuria, haematuria, & abdominal pain	No metastasis	He had a histor y of imma ture terato ma; his seru m α - fetopr otein was 192 ng/ml (nor mal range < 20 ng / ml); his seru m β - Hum an chori	Varia bly sized gland s whic h were lined either by matur e or imma ture intest inal, respir atory, and neuro ne epith elial, imma ture chon droid	At the begin ning he was treate d for imma ture terato ma by mean s of bleo myci n, etopo side, and cispla tin chem other apy; never theles	He was alive and free of disea se at 16 mont hs follo w-up	

			onic gona dotro phin was 11.6 mIU / ml (nor mal range < 5 mIU / ml).	tissue , matur e adipo se tissue , and atypi cally non- prolif eratin g endot helial cells whic h had spora dic large, hyper chro matic nucle i, and frequ ent mitoti c figure s typic al of inter medi ate grade angio sarco ma. The	s, the tumo ur mass conti nued to grow; he then under went radic al cysto prost atecto my and forma tion of an ileal cond uit.		
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				tumour on immunohistochemistry stained positive for CD31 and CD34.			
Guo et al. [8] 2009	65 years; haematuria & intractable perineal pain.	No metastasis	He had a history of Gleason 3+3 = 6 adenocarcinoma of the prostate gland which was treated by means of androgen ablation and radiotherapy.	A vasofornate growth in which had complex anastomosing channels was seen on histological examination, the tumour cells had	Total pelvic exenteration in which the surgical resection margin was found to be positive for tumour.	He died at 8 months.	

			y 4 years preceding his presentation. His serum PSA test at presentation with PAS OP showed undetectable PSA	highly atypical nuclei that had robust mitotic activity. The tumour exhibited positive immunohistochemical staining for CD31 and CD34			
Khaliq et al. [9] 2012	73 years; haematuria, diurnal urinary frequency and nocturia.	No metastasis	He had a history of adenocarcinoma of prostate Gleason 3 + 3 = 6	Proliferating vascular channels were seen on histological exam	He underwent total pelvic exenteration and it was noted that the urinar	He died at 9 months	

			which had been treated by means of external beam radiotherapy and brachytherapy boost 8 years preceding the diagnosis of his PAS OP. His serum PSA at the time of the diagnosis of PAS OP was 1.2 ng / ml	injection and these channels were lined by atypical and malignant appearing endothelial cells, which were adjudged to be consistent with high grade angiosarcoma. The tumour cells on immunohistochemistry exhib	ly bladder, and seminal vesicles were directly involved by the tumour extension. During the cystoprostatectomy the tumour was observed to be present the urethral margin and the left anterolateral		
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			(with normal range).	ited positive staining for factor VIII and CD31. The tissue had been extensively infiltrated by atypical cells that had active mitotic activity.	pelvic sidewall. The surgical margins were positive for angiosarcoma and six of the nine pelvic lymph nodes were positive for metastatic adenocarcinoma of the prostate gland with extra-nodal extension		
Humphrey et al.	67 years; urinary tract obstructive	Presence or absence of	He had	Histologic	TURP for	Long term	

[41] 2012	symptoms	metastasis not mentioned in paper and it would be presumed there was no metastasis.	radiot herap y for carci noma of the prost ate gland 7 years prece eding the diagn osis of his PAS OP	al exam inatio n show ed a neopl astic spind le proliferatio n whic h forme d irregu lar vascu lar chann els whic h ad disse cted throu gh the strom a of the prost ate and urinar y bladd er. Other areas of the	lower urinar y tract symp toms	outco me not report er; case was report er not long after the TUR P	
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				tumour were more solid and admixed with the vascular spaces. The vascular channels were lined by neoplastic endothelial cells which had displayed nuclear atypia. The tumour cells on immunohistoche			
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				mical staini ng staine d posit vely for CD31 , CD34 , and Facto r VIII- relate d antig en. The was no evide nce of any resid ual adeno carci noma of prost ate and immn unohi stoch emist ry had show n			
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				negative staining for pan-cytokeratin, prostate specific antigen, and prostate specific acid phosphatase which together confirmed the diagnosis of PAS OP and absence of adenocarcinoma of prostate			
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				ate.			
Campschroer et al. [40] 2014			Angi osarc oma of prost ate in patie nt who previ ously had brach yther apy for adeno carci noma of prost ate				
Gupta et al. [43] 2014	71 years; lower urinary tract symptoms and visible haemturia.		The patie nt had radiot herap y to the prost ate as treat ment for an incid entall y diagn osed				

			Gleason 3 + 3 = 6 adenocarcinoma of the prostate based upon routine serum PSA of 4 ng/ml investigation 5 years prior to the diagnosis of PAS OP				
Scharpira et al. [44] 1963	Details not available	Details not available	Details not available	Details not available	Details not available	Details not available	
Wick et al. [45] 1989	69 years; details not available	Details not available	Details not available	It was a carcino- carcinoma with other	Details not available		

				types of sarco ma			
Russo et al. [46] 1992							
Loque Barona et al. [47] 2000							
Boucher et al. [48] 2000							

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