Archives of Clinical & Experimental Surgery

Original Article

Arch Clin Exp Surg 2018;7:94-99

doi:10.5455/aces.20170921120541

eJM eJManager OPEN ACCESS

Post-radiation pelvic sarcomas after radiotherapy treatment of prostate adenocarcinoma

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ABSTRACT

Background: The number of publications reporting the appearance of post-radiation secondary tumors has increased in parallel with the development of radiotherapy. However, little information is available about the presence of sarcomas associated with prostate radiotherapy.

Objective: To review cases of pelvic sarcoma associated with prostate radiotherapy in a tertiary hospital.

Methods: Following the criteria established by Cahan, 11 pelvic sarcoma patients with a history of radiotherapy treatment of prostatic adenocarcinoma between the years 2006 to 2016 were identified. A descriptive study was designed to review the characteristics of patients, tumors, therapy administered, and its effect on the outcome of the cancer.

Results: The average age of patients upon diagnosis was 72.27 years (60-79), with an average latency time of 6.27 years (4-9 years) between radiotherapy and diagnosis of sarcoma. The mean radiotherapy dose was 74Gy (70-78). The most common location of the sarcoma was regions II-III of the pelvic girdle (72%), followed by the pelvic cavity. The main histological type was undifferentiated pleomorphic sarcoma (54%); two patients presented metastases at the time of diagnosis. In total, 81.8% of patients were treated surgically with curative intent, and of these, seven received adjuvant chemotherapy. Mean follow-up was 14 months, with a two-year survival rate of 18.2%.

Conclusion: Given the poor prognosis of post-radiation pelvic sarcomas, efforts must be made to establish protocols for early diagnosis and to develop aggressive, standardized treatment guidelines.

Key words: *Post-radiation, sarcoma, prostate adenocarcinoma*

Introduction

Post-radiation sarcoma is the name given to connective tissue tumors that develop secondary to exposure to ionizing radiation. The number of publications reporting the appearance of post-radiation secondary tumors has increased in parallel with the development of radiotherapy (RT). Sarcomas are among the first solid tumors to be associated with this exposure [1,2]. Between 0.1%-5% of patients treated with radiotherapy will develop a second tumor, but only 5% are considered to be directly therapy-related [3,4].

The criteria to define a post-radiation sarcoma was initially established by Cahan, et al., in 1948, and later reviewed by Arlen, et al., in 1971[5] and Murray, et al., in 1999[6-8]: history of microscopic or radiographic signs of non-malignant neoplasm or non-osteoblastic

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Received / Accepted : *September 21, 2017 / November 02, 2017*

tumour prior to administration of radiation; administration of radiation therapy and subsequent formation of a tumor within the field of previous therapeutic irradiation; relatively long asymptomatic latency period (8-12 years) culminating with the appearance of a sarcoma histologically different from the treated tumour and no clear biological factors that would explain the asymptomatic period. Almost half of these sarcomas result from radiation of adjacent healthy tissue[9], but as no relationship between the radiation dose and the latency period or frequency of sarcomas has been established, the development of secondary tumors is considered to be a late stochastic effect[3].

Prostate cancer is the most common non-cutaneous solid tumor in men [4,10]. Radiotherapy is often used to treat this malignancy and is indicated at every stage free of metastatic involvement. According to Bostrom, et al.[11], one in 70 patients with prostate cancer treated with RT will develop a secondary tumor if they survive more than ten years, but only 0.16% of these are considered therapy-induced [12]. Standard radical RT treatment schedules involve two treatment phases to deliver a total dose of 78Gy in the prostate. Pelvic tissues receive between 50%-65% of the total dose, 39-50Gy, and the dose administered to periprostatic structures such as the bladder or rectum is even higher.

This study aims to define the characteristics and prognosis of pelvic sarcomas in patients with a history of radiotherapy treatment of prostate adenocarcinoma.

Material and Methods

A retrospective study was performed after identifying all patients diagnosed with pelvic sarcoma between 2006 and 2016. We obtained a sample of 11 patients with a history of prostate adenocarcinoma treated with radical radiotherapy that met Cahan's diagnostic criteria. The present study was carried out following approval by the local Ethics Committee (code: SARCOMASRT, 15th August 2017) and all patients gave their written consent for inclusion in the study.

All patient demographic data were collected, together with the characteristics of the prostate adenocarcinoma, date of diagnosis, Gleason and TNM stage, type of radiotherapy (date of administration, number of sessions, dose) and overall treatment for the disease. Data relating to the pelvic sarcoma included: date of diagnosis, latency time, location, TNM stage, pathology, and treatment administered. In patients with skeletal involvement treated with curative intent, an internal or external hemipelvectomy was performed, based on the likelihood of obtaining a tumor-free resection margin and estimated postoperative limb function.

The presence of complications was also recorded: immediate complications were defined as those arising in the first postoperative month, and deferred complications were any arising after that. Other data recorded were follow-up time, local or distant recurrence, and survival. Functional results were recorded at three and six months and one and two years after surgery.

Data were processed using SPSS Statistics® version 22.0 for Mac (IBM, NY, USA). Survival was analyzed using Kaplan-Meier curves.

Results

A total of 11 patients with a mean age of 72.27 years (60-79) were included in the study. All had a history of radical radiotherapy for prostate adenocarcinoma, with an average radiation dose of 74Gy. In four patients, radiotherapy was combined with hormonal therapy, and in two with radical prostatectomy.

Mean latency to the appearance of post-radiation sarcoma was 6.27 years, a minimum four years and a maximum nine years. The most common site was the pelvic ring, in 72% of cases, in the remaining 28% the tumor was located in the pelvic cavity: two visceral and one retroperitoneal (Figure 1).

The most common histological type was undifferentiated pleomorphic sarcoma (UPS), in six cases (54%), followed by osteosarcoma in three cases (27%), one case of chondrosarcoma and one of leiomyosarcoma. All (100%) sarcomas were histologically classified

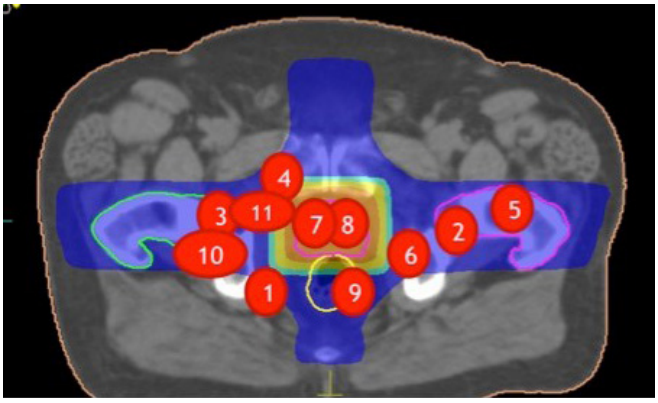

Figure 1. Sarcoma location in relation to radiotherapy field.

Table 1. Treatment of postradiation sarcomas.

	Surgical treatment	Margins	IORT	CT
1	Internal hemipelvectomy (IIA + III)	R0	No	Adjuvant
2	Internal hemipelvectomy (IIA + III)	R1	Yes	Neoadjuvant
3	Internal hemipelvectomy (IIA + III)	R0	No	Neoadjuvant
4	Extended resection	R1	Yes	No
5	Extended resection	R0	No	No
6	Extended resection	R0	No	No
7	Local resection	R0	No	Neoadjuvant
8	Internal hemipelvectomy (IIA + III)	R1	No	Adjuvant
9	Internal hemipelvectomy (II + III)	R0	No	Adjuvant

IORT: intraoperative radiotherapy, CT: chemotherapy.

as high grade according to the FNCLCC histological grading system. A total of 63.6% of patients presented locally advanced stage, and the remaining 36.3% distant disease at diagnosis, with lung metastasis in three cases and one case of a vertebral location at the level of D11.

Regarding treatment, nine patients (81.8%) were treated with curative intent, and the other two received palliative chemotherapy (Table 1). Five patients underwent surgery combined with chemotherapy - neoadjuvant in three cases and adjuvant in two cases. In two patients, surgery was combined with intraoperative radiotherapy. Complications occurred in eight of nine patients treated surgically. The main early complications were postoperative neuropathy and wound infection (36.3%), which was resolved in all cases with cleaning and debridement. The most frequent late complication was the deep infection, manifesting as cutaneous fistula in 36.3% of cases. This was resolved with specific antibiotic therapy and adequate cleaning and debridement (Table 2).

All study patients were followed up from diagnosis of sarcoma until exitus or the present, with no losses to follow-up. Mean follow-up was 14 months. Five (45.4%) study patients presented local recurrence during follow-up, three of these underwent surgical treatment, in one of which external hemipelvectomy was later required despite initial limb-sparing surgery. Two treated patients presented distant recurrence with lung metastasis at seven and 30 months of follow-up.

Table 2. Complications.

Early complications (<1 month)	N
Wound infection	4
Sciatic nerve palsy	3
Septic shock	2
Haemorrhagic shock	2
Urethral fistula	2
PE	2
Intestinal obstruction	2
Perioperative coagulopathy	1
Retroperitoneal abscess	1
Acute renal failure	1
Common iliac artery pseudoaneurysm	1
Skin coverage defect	1
Late complications (>1month)	
Skin fistula	3
Iliac vein thrombosis	1
Renal insufficiency	1
Vesical fistula	1
Osteomyelitis	1
Scrotum ulcer	1

PE: pulmonar embolism

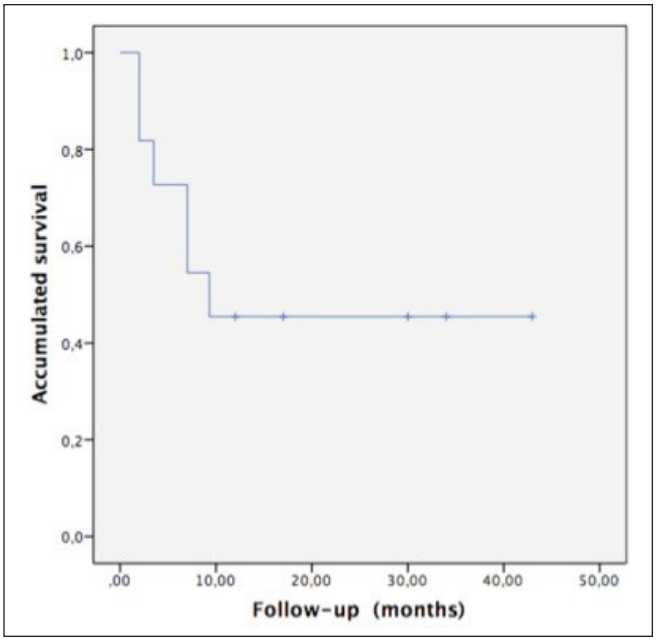

Figure 2. Kaplan-Meier survival analysis.

Survival analysis showed the median overall survival of 15.48 months, a minimum two and a maximum 43 months. The one-year survival rate of patients treated with curative intent was 55.5%, with a mean survival of 16 months (Figure 2), whereas survival was 5.75 months in non-treated patients.

Discussion

The relationship between radiation therapy and development of sarcomas has been studied in locations such as the breast or cervix [13-15], but only isolated cases of post-radiation sarcoma secondary to prostate adenocarcinoma have been reported in the literature. This series, therefore, could be considered the most extensive conducted to date in this pathology [16-18]. The risk of developing sarcoma following radiotherapy treatment is estimated at between 0.03% and 0.8% [19,20].

Although evidence suggests the existence of a minimum radiation dose required to induce bone sarcoma, this threshold has yet to be established. In their cohort study, Martland and Humphries [21] observed that all cases of sarcoma detected occurred in patients exposed to a dose more than 10 Gy, while Kalra et al., [3] reported a median estimated radiation of 20Gy. Recent studies have shown that doses above 30Gy are more closely correlated with the appearance of sarcoma. This was the dose received by 100% of our patients treated with radical radiotherapy for prostate adenocarcinoma [1,22]. Kalra et al. [3], analyzing the latency time of post-radiation sarcomas, ruled out a correlation between radiation dose and latency period until the appearance of radiation-induced sarcoma.

Although the molecular pathways involved in the development of post-radiation tumors remain unclear, studies have shown that these second tumors are histologically indistinguishable from the primary neoplasm[20]. Several authors consider osteosarcoma to be the most common histologic type of post-radiation sarcoma, with an incidence rate of 50%-60% [3,23,24]. In our study, however, it took second place to undifferentiated pleomorphic sarcoma, which was found in 54% of cases.

There is a general consensus on the poor outcome associated with malignant pelvic sarcomas [3]. Tumours in this location are usually larger at the time of diagnosis, and resection is more complex and often requires a multimodal strategy. The poor prognosis associated with the pelvic location is further aggravated by the poor prognosis associated with previous tumor bed radiation [25]. Some series have shown maximum survival rates of 15% [24], compared to 50%-80% in primary sarcomas [26,27]. Although surgical treatment of secondary pelvic sarcomas does not have a cumulative effect concerning the first intervention, evidence has shown that effectiveness of chemotherapy treatment schedules may be severely undermined by prior exposure to cytotoxic agents and the subsequent development of resistance to these drugs [9,28-31]. Moreover, many of these post-radiation tumors are considered resistant to radiotherapy, and therapeutic outcomes are disappointing.

Recent studies [24,32] suggest that, with early diagnosis and aggressive medical and surgical treatment strategies, such as those adopted in our study, the survival rate of patients suffering from "secondary" sarcomas can approach that of primary sarcomas, describing a median survival of 12 months [24,32], which is similar to that observed in our study.

Other poor prognostic factors have been identified, in addition to the post-radiation origin of the tumor. Advanced age is considered a poor prognostic factor, although no precise breakpoint has been established. Kalra et al. [3], associated age > 40 years with poor prognosis, while Al-Refaie et al. [33], set the breakpoint at > 65. Pelvic location of the post-radiation sarcoma reduces overall survival from 66%-68% to 28.5%, according to Sim et al. [25].

This is largely due to the difficulty of achieving adequate resections. We would point out that, in our study, 82% of patients were aged 65 or older at the time of sarcomas' diagnosis, and that the mean age at the start of radiotherapy for prostate cancer was 66 years. In other words, our series was already burdened with two poor prognosis factors at the time of diagnosis: pelvic location and age.

Conclusion

The poor overall survival of post-radiation pelvic sarcomas has been widely described. Further studies are needed to clarify the molecular pathways involved in the development of these tumors and the risk factors determining their evolution. This will enable us to address the two most pressing issues surrounding this pathology: the need for an early diagnosis protocol in high-risk patients, and the need for standardized, aggressive surgical or chemotherapy or radiotherapy treatment guidelines.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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