Adult prostatic sarcoma: A contemporary multicenter Rare Cancer Network study

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Introduction: Adult prostatic sarcoma (PS) is a rare disease. While surgery is considered the standard approach, the role of other therapies is not completely established. We report results of the largest multicentric contemporary cohort of PS patients.

Materials and Methods: This study included 61 adult PS patients treated in 16 American and European Institutions. Median age was 64.4 years (range: 22-87). Curative surgery was delivered in 48 patients (prostatectomy = 26, cystoprostatectomy = 22), usually with lymphadenectomy (n = 40). Curative radiotherapy (RT) was delivered in 32 patients, as radical (n = 5), neoadjuvant (n = 10), or postoperative treatment (n = 17). Eighteen patients received chemotherapy. None of the patients received hormonal therapy.

Results: Median follow-up was 72 months (95%CI: 55-not reached). Five-year local control (LC), overall survival (OS), cancer-specific survival, disease-free survival, and metastases-free rates were 47%, 53%, 56%, 35%, and 35%, respectively. Notably,
Curative RT (neoadjuvant, adjuvant, or definitive) was associated with improved 5-year LC (55% vs. 31%, \( P = 0.02 \)) and OS (59% vs. 46%, \( P = 0.1 \)). Surgically treated patients presenting with a cT3-4 tumor \( (n = 31) \), who received RT \( (n = 24) \), had a significantly improved 5-year LC (68% vs. 33%, \( P = 0.004 \)) and OS (65% vs. 21%, \( P < 0.001 \)) rates compared to patients not receiving RT. cT4 patients demonstrated a significantly lower 5-year OS (43% vs. 61%, \( P = 0.006 \)) and LC (29% vs. 69%, \( P < 0.001 \)) rates. Histologic subtype was not associated with LC and OS, but patients with prostatic stromal sarcoma, rhabdomyosarcoma, or sarcomatoid carcinoma had worse 5-year LC compared to other types (47% vs. 55%) and OS (49% vs. 58%).

**Conclusion:** Adult PS has a poor prognosis. Locally advanced tumors have poor LC and OS rates. Curative RT should be considered part of the multidisciplinary approach to PS.

**Keywords**
chemotherapy, multimodal treatment, prognostic factors, prostatic sarcoma, radiotherapy, surgery

1 | INTRODUCTION
Prostatic sarcoma (PS) is an extremely rare type of adult non-epithelial malignant tumor, accounting for only 0.1-0.2% of all prostate cancers.\(^1\) Surgery is considered the standard therapeutic cornerstone,\(^2\)–\(^4\) similar to the approach for other sarcomas. However, surgery alone seems to obtain poor results when compared to multidisciplinary approaches.\(^3\) Nevertheless, given the rarity of PS, optimal therapy is debatable. The role of neoadjuvant and adjuvant treatments (radiotherapy [RT], chemotherapy) is not defined, and the indications are often based on institutional preference or by analogy with soft tissue sarcoma (eg, limb or retroperitoneal) recommendations. Data from the available literature are limited: the number of patients is often small (4-23 patients), often including also metastatic situations,\(^3\)–\(^7\) diagnostic and treatment modalities are often inhomogeneous, and some patients were likely treated in different eras (eg, >60 years prior)\(^5\). This influences the analysis of clinical outcomes and the choice of the therapeutic approach to PS.

The Rare Cancer Network (RCN, www.rarecancer.net) supports cooperative research projects about rare tumors which could be studied by multicenter retrospective data collection studies.\(^8\) In February 2016, the RCN launched a multicenter study aiming at the data collection of adult patients treated for a PS. Aim of this work was to characterize treatment strategies, natural history, and outcomes of patients with PS.

2 | MATERIALS AND METHODS
In February 2016, a letter describing the project was sent to 27 American and European institutions members of the RCN. Ultimately, 16 centers (6 American, 10 European) agreed to participate in this retrospective study. They were asked to anonymously report demographics, clinical, and therapeutic data of their adult patients (>18 years old) treated for histologically proven non-metastatic PS, in a common database. All histologic subtypes and therapeutic approaches were accepted. Sarcomas arising from seminal vesicles were excluded.

Data were collected using hospital electronic records and charts, updated to the date of this analysis (December 8, 2016). We performed a descriptive analysis of the whole population. Local control (LC) and overall survival (OS), disease-free survival (DFS), cancer-specific survival (CSS), and metastases-free survival (MFS) rates were calculated, using the date of biopsy as initial reference date. Events were local relapse (LR), death from any cause (OS) or from cancer (CSS), death from any cause or any relapse (DFS), and death from any cause or the diagnosis of metastases (MFS). Dates of death were confirmed using death certificates. In case of clinical or pathologic evidence of active, recurrent disease, without any information about the cause of death, we attributed deaths to PS. LR was defined as any clinical and/or radiologic evidence of locally relapsing or progressing tumor. Follow-up time was calculated using the method described by Schenper et al.\(^9\) To prevent immortal time bias, all patients needed have been alive for at least 1 month after surgery. Fisher’s exact test for values of less than 5 or chi-square test for values more than 5 was used to compare proportions. The Kaplan-Meier method was used to estimate the survival, and the log-rank test was used to compare the impact of clinical or therapeutic variables. Confidence intervals (CI) were computed from standard errors, and a \( P < 0.05 \) was considered significant. The Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL) was used for statistics. Study data collection protocol was designed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the independent ethics committees at all participating hospitals.
3.1 | Population

Sixty-one patients respecting the inclusion criteria were retrospectively collected. Forty patients were treated in American Institutions and 21 in European ones. Patients were diagnosed in the period between January 1987 to February 2016. Table 1 summarizes the features of the whole population. Median age at diagnosis was 64.4 years (range: 22-87). Most of patients presented with urinary symptoms ($n = 35, 56\%$).

All but seven patients underwent a whole-body computed tomography scan for local and systemic staging of the disease. Endorectal ultrasound and pelvic magnetic resonance imaging (MRI) were performed in 27 and 28 patients, respectively. Transurethral prostatic resection ($n = 26$) and prostate biopsies ($n = 22$) were the most commonly used modalities to obtain the histological diagnosis. Leiomyosarcoma ($n = 18$) and PS not otherwise specified (NOS, $n = 17$) represented the most common diagnoses. Patients were retrospectively re-staged using the 7th edition Union International Contre le Cancer (UICC) 2009 tumour node metastasis (TNM) classification staging system for the prostate adenocarcinomas.\textsuperscript{10} Sarcoma TNM staging system was not used as it was not possible to obtain the diameter of the tumors for many of the included patients.

Thirty-eight patients presented with locally advanced tumor at the time of the diagnosis ($cT3a-b$ or $cT4$), and four with a regional involvement ($cN+$ or $pN+$).

3.2 | Treatment details

Table 2 summarizes data about the treatments delivered to the patients. Fifty-three patients were treated with a curative intent, and 27 of them received a multimodal approach. Surgery was delivered with a curative intent in 48 patients, usually with lymphadenectomy ($n = 40$). Twenty-six patients received a prostatectomy, and 22 a cystoprostatectomy. Of them, 27 also received RT, as neoadjuvant ($n = 10$) or adjuvant treatment ($n = 17$). RT details are summarized in Table 2. Globally, 18 patients received chemotherapy, mostly concomitantly and as adjuvant treatment to postoperative RT ($n = 11/18$).
3.3 Outcomes

3.3.1 Whole population

Median follow-up was 72 months (95%CI: 55-not reached). Five-year LC, OS, CSS, DFS, and MFS rates were 47% (95%CI: 33-62%), 53% (95%CI: 39-67%), 56% (95%CI: 42-70%), 35% (95%CI: 21-49%), and 35% (95%CI: 20-50%), respectively. Figures 1 and 2 show LC and OS for the whole population.

Patients who received RT with a curative intent (i.e., in a neoadjuvant, or adjuvant, or a radical setting) presented a significantly improved 5-year LC (55% vs. 31%, \( P = 0.02 \)), and an improved OS (+13 points, 59% vs. 46%, \( P = 0.01 \)).

Patients treated with a curative multimodality treatment (surgery and/or RT±chemotherapy) demonstrated an improved 5-year LC (59% vs. 13%, \( P = 0.009 \)) and 5-year OS (59% vs. 28%, \( P = 0.02 \)) compared to those treated palliatively. Additionally, a strong trend

### TABLE 2 Treatment characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Modality of treatment</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>Curative prostatectomy</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Curative cystoprostatectomy</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Palliative surgery</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Only transurethral resection of the prostate (TURP)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No surgery</td>
<td>6</td>
</tr>
<tr>
<td>Radiotherapy⁹</td>
<td>Radical</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Median dose: 60 Gy (range: 55.8-74 Gy, 1.8-2.25 Gy/fraction)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjuvant</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Median dose: 59.4 Gy (range: 10-70.2 Gy, 1.8-2 Gy/fraction)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Median dose: 50 Gy (range: 5-58 Gy, 1.8-2 Gy/fraction)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Only chemotherapy</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Curative adjuvant (after surgery)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Curative adjuvant (after radiotherapy)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Curative concomitant and adjuvant to radiotherapy</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant to surgery (always followed by adjuvant radiotherapy)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>No chemotherapy</td>
<td>43</td>
</tr>
</tbody>
</table>

⁹Only one patient received pelvic RT (45 Gy, 1.8 Gy/fraction). Data on RT plans were not available for one patient treated with surgery and adjuvant RT. Two patients presented a rapid degradation of their performance status after 5 Gy and 10 Gy, respectively, and did not finish their treatment. In order to avoid selection bias, these two patients were included in the RT group for our statistics.
toward improved 5-year CSS was seen in patients receiving a curative approach (+40 points, 62% vs 22%, $P = 0.2$).

Histologic type did not significantly influence the LC and OS, but patients presenting a prostatic stromal sarcoma, rhabdomyosarcoma, or sarcomatoid carcinoma showed a slight trend toward a worse 5-year LC compared to other types (47% vs. 55%) and OS (49% vs. 58%).

3.3.2 | Results of multimodality approach

Curative surgery was delivered in 48 patients. Of these patients, 27 received RT either as an adjuvant ($n = 17$) or neoadjuvant treatment ($n = 10$), and 13 received also chemotherapy (see Table 2).

Globally, RT improved 5-year LC (+29 points, 69% vs. 40%, $P = 0.13$) and OS survival rates (+12 points, 60% vs. 48%, $P = 0.13$), when compared to surgery alone.

In cT3-4 patients ($n = 31$), RT ($n = 24$) significantly improved 5-year LC (68% vs. 33%, $P = 0.004$, Fig. 3) and OS (65% vs. 21%, $P < 0.001$, Fig. 4). RT did not influence OS or LC in the 4/17 cT1-T2 patients who received RT.

Chemotherapy improved the 5-year OS (+12 points, 68% vs. 56%, $P = 0.8$) and LC (+11 points, 72% vs. 61%, $P = 0.1$). The 5-year MFS was 36% in patients who did not receive chemotherapy and 66% in patients who received it ($P = 0.6$). All these differences are not statistically significant.

Patients presenting with a T4 tumor ($n = 14$), 5-year LC (29% vs. 69%, $P < 0.001$) and OS (43% vs. 61%, $P = 0.006$) were significantly worse when compared to cT1-3 patients ($n = 34$). No differences were seen when we compared cT1-2 and cT3-4 patients.

4 | DISCUSSION

To the best of our knowledge, we report the largest series of PS patients. In this multicenter, retrospective study after a median follow-up of 72 months, we found 5-year LC, OS, CSS, DFS, and MFS rates of 47%, 53%, 56%, 35%, and 35%, respectively. Additionally, we found that multimodal therapy (typically surgery and RT) is associated with improved outcomes.

PS is a rare and lethal cancer: a rough comparison of the survival data relative to the more common prostatic adenocarcinoma demonstrates significantly worse LC and OS rates for patients with PS. In the available studies, more than 95% of the patients who had died at the last follow-up, had died as a result of PS. Moreover, given the rarity of this aggressive tumor, prospective trials are unlikely, and the ideal treatment paradigm is unknown, in particular concerning the role of adjuvant and neoadjuvant treatments.

Given its retrospective and multicentric nature, our study has some important limitations. Looking at the treatment approaches, the choice of prostatectomy or cystoprostatectomy varied considerably, as did neoadjuvant and/or adjuvant treatments which consisted of RT±chemotherapy. The population was composed of patients with heterogeneous disease stages and follow-up was not accomplished in a prospective manner. Data on toxicity are lacking. The only severe side effect reported was in one patient, who received preoperative RT and cystoprostatectomy, and who died in the immediate postoperative setting because of surgical complications. No other data about toxicity were reported by the participating institutions.

Nevertheless, our series shares the same limits of other PS series previously published. Moreover, all the patients have been treated in a more contemporary period (1987-2016) than other published studies, and the results are therefore more applicable for the current clinical practice. Thus, this multicenter cohort provides interesting information to help guide patient management for this rare diagnosis.

Our modern series seems to show slightly better LC and OS rates compared to the largest existing published series (see Table 3). Compared to our study, these reports usually consisted of larger tumors at diagnosis, probably because in the more recent decades men are being more aware about the importance of urinary symptoms for
Principal studies reporting data on prostatic sarcoma patients

<table>
<thead>
<tr>
<th>Author, reference</th>
<th>Treatment period</th>
<th>No. of patients</th>
<th>Most common histology (% of patients)</th>
<th>FUP (years)</th>
<th>LC (%)</th>
<th>OS (%)</th>
<th>DFS (%)</th>
<th>MFS (%)</th>
<th>Prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dotan et al.12</td>
<td>1977-2003</td>
<td>21</td>
<td>Rhabdomyosarcoma (43)</td>
<td>2.6 (mean)</td>
<td>NA</td>
<td>39</td>
<td>24</td>
<td>NA</td>
<td>Tumor size (&lt;5 cm)</td>
</tr>
<tr>
<td>Ball et al.11</td>
<td>1993-2013</td>
<td>8</td>
<td>NR</td>
<td>2.8 (median)</td>
<td>100</td>
<td>55.6</td>
<td>22.2</td>
<td>NR</td>
<td>Metastatic disease at diagnosis</td>
</tr>
<tr>
<td>Sexton et al.3</td>
<td>1972-2000</td>
<td>21</td>
<td>Leiomyosarcoma (57)</td>
<td>NA</td>
<td>19/21a</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>Negative surgical margins</td>
</tr>
<tr>
<td>Cheville et al.2</td>
<td>1929-1994</td>
<td>14</td>
<td>Leiomyosarcoma (100)</td>
<td>1.6 (mean)</td>
<td>NA</td>
<td>10 of 14 cancer-related deaths</td>
<td>One out of four alive patients was disease free</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Musser et al.13</td>
<td>1982-2012</td>
<td>38</td>
<td>Leiomyosarcoma (34)</td>
<td>4.1 (for alive patients)</td>
<td>NR</td>
<td>CSS: 7.7 years</td>
<td>NR</td>
<td>NR</td>
<td>For CSS: Stage IV rhabdomyosarcoma; For RFS: Stage IV</td>
</tr>
<tr>
<td>Present study</td>
<td>1987-2016</td>
<td>61</td>
<td>Leiomyosarcoma (30)</td>
<td>6 (median)</td>
<td>47 (5 years)</td>
<td>53 (5 years)</td>
<td>47 (5 years)</td>
<td>35 (5 years)</td>
<td>T4 tumors and palliative approach (poor prognostic factors)</td>
</tr>
</tbody>
</table>

FUP, follow-up; LC, local control; OS, overall survival; MFS, metastases-free survival; NR, not reported; CSS, cancer-specific survival; RFS, relapse-free survival.

*Last follow-up status.

**It was 38% in the whole population but the authors presented data on metastatic and non-metastatic patients. In this table, we report the 5-year actuarial OS rate of non-metastatic patients, as it is more comparable with our population.

*Authors report data on median CSS. In their article, it was of 2.9 years, but the authors presented data on metastatic and non-metastatic patients. In this table, we report data on median CSS of non-metastatic patients, as it is more comparable with our population.

**In the study by Sexton et al., six patients received surgery after neoadjuvant treatments, with all demonstrating more than 90% necrosis of primary tumors. The combination of surgery and adjuvant RT in patients who received neoadjuvant RT was considered a strong point of the study.

In some of the available studies, potential prognostic factors for CSS in a large population of patients presenting with OS and CSS were both 65.5%.

As previously published, our study confirmed that the presence of metastatic disease at diagnosis was a poor prognostic factor (HR: 5.91, 95%CI: 2.31-15.11, P = 0.0002).
These authors also showed that rhabdomyosarcoma patients have the poorest CSS compared to leiomyosarcomas patients (HR: 3.00, range: 1.13-7.92, \( P = 0.027 \)). Sexton et al.\(^7\) reported data on 21 adult PS patients: in their analysis, negative surgical margins \( (P = 0.0005) \) and the absence of metastatic disease at presentation \( (P = 0.0004) \) were positive prognostic factors for CCS, while tumor size, tumor grade, and histological subtype did not influence survival.\(^3\) Note-worthy, these results could be influenced by the very unbalanced populations: 12 of 21 patients presented a leiomyosarcoma, while only five presented a rhabdomyosarcoma. Only five patients showed metastatic spread at diagnosis, and only three patients presented a microscopic or a macroscopic residual disease after surgery. In the study by Cheville et al.,\(^5\) only adult leiomyosarcoma patients were included, and no specific analyses were performed to find any prognostic factor. In our study, only non-metastatic patients were included; our results showed the worst results in patients presenting a T4 tumor compared to those presenting a T1-T3 tumor. Histology did not influence OS, CSS, or LC. The only factor improving the outcome was the receipt of a curative intent treatment and, in those treated with a curative goal and presenting a more advanced disease, a multidisciplinary approach involving local irradiation.

5 | CONCLUSIONS

Our results confirm that the prognosis of PS is poor, and that the pattern of relapse is principally systemic. Multimodal therapy with surgery and RT is associated with improved outcomes versus either approach alone. The role of chemotherapy seems promising, and deserves further investigations in this particular setting.

CONFLICT OF INTEREST DISCLOSURE AND FUNDING DECLARATION

No conflict of interests exists. Authors have not received funds for this research.

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