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Original Article

The management of retroperitoneal sarcoma: The experience of a single institution and a review of the literature

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الملخص

اهداف البحث: تعتبر الساركوما خلف الصفاق من اورام اللحمة المتوسطة النادرة. تهدف هذه الدراسة الى مناقشة مختلف الجوانب السريرية العلاجية، والإنذارية للساركوما خلف الصفاق التي تم علاجها في مؤسستنا.

طرق البحث: تم اجراء دراسة مرجعية في قسم الأورام الطبية المستشفى الجامعي مستشفى جامعة الحبيب بورقيبة في صفاقس، تضمنت ١٩ مريضا عولجوا من الساركوما خلف الصفاق بين عامي ١٩٩٩ و٢٠١٦

النتائج: كان متوسط العمر ٤٩ عاما (يتراوح بين ١٨-٨٣). لوحظ ان غالبيتهم من الإناث (٦٨,٤٪). كانت الأعراض الأكثر شيوالما البطن (٨٨٪). كان متوسط حجم الورم ١٥ سم (٤-٣٠ سم). تم الاستئصال الكامل في خمس حالات فقط (٢٦,٣٪). كانت الأنواع الفرعية النسيجية الاكثر شيوعا الساركوما الشحمية (٤٧,٤٪) والساركوما العضلية (٢٦,٣٪). كان لدى ثمانية من المرضى ورم عالي الدرجة (الدرجة ٢=٢ أو الدرجة ٣=٦). تم إعطاء العلاج الإشعاعي المساعد ٥ من المرضى (٢٦٪). تم علاج سبعة عشر مريضا بالعلاج الكيميائي، ستة منهم اخذوه في وضع مساعد، ثلاثة كعلاج جديد، وثمانية في المرحلة التلطيفية. لوحظ عودة المرض لدى ٥٨٪ من الحالات. في جميع المرضى، كانت النجاة بشكل عام ٨٩,٥٪ في العام الأول و٤٠,٣٪ بعد خمسة أعوام. كانت عوامل النذير التي أثرت على النجاة بشكل عام نوع الجنس، حدود الاستئصال، عودة المرض، والعلاج الإشعاعي. في التحليل متعدد المتغيرات، كان العلاج الإشعاعي ونوع النسيج الفرعي عوامل مستقلة تؤثر على النجاة بشكل عام والنجاة خاليا من المرض على التوالي

الاستنتاجات: في هذه الدراسة، تبين أن علاج الساركوما خلف الصفاق يعتمد على الجراحة مع الاستئصال التام. العوامل الأخرى مثل العلاج الإشعاعي ومعاودة المرض لها تأثير على النجاة بشكل عام. لتسهيل الجراحة والحصول على حدود استئصال سالبة، يفضل العلاج الإشعاعي قبل الجراحة على مرضى معينين لديهم خطورة عالية للانتكاس. المزيد من المحاولات المستقبلية لها ما يبررها لاختيار العلاجات المثلى بأقل سمية وأفضل فعالية لتقليل عودة المرض، بشكل رئيسي موضعي

الكلمات المفتاحية: الساركوما الشحمية؛ التنبؤات؛ ساركوما خلف الصفاق؛ الاستئصال؛ النجاة

Abstract

Objectives: Retroperitoneal sarcomas (RPSs) are rare mesenchymal tumors. The objective of this study was to discuss the different clinical, therapeutic and prognostic aspects of RPS in our institution.

Methods: This was a retrospective study conducted at the Department of Medical Oncology in the Habib Bourguiba University Hospital in Sfax, including 19 patients who were treated for RPSs between 1999 and 2016.

Results: The median age was 49 years (range: 18–83 years); 68.4% of the patients were female. The commonest symptom was abdominal pain (88%) and the median tumor size was 15 cm (range: 4–30 cm). Complete resection was achieved in only five cases (26.3%). The most common histological subtypes were liposarcoma (47.4%) and leiomyosarcoma (26.3%). Eight patients had a high-grade tumor (G2 = 2 or G3 = 6). Adjuvant radiotherapy was administered in 5 patients (26%). Seventeen patients were treated with

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chemotherapy; six received chemotherapy in an adjuvant treatment, three as a neoadjuvant treatment, and eight were treated during the palliative phase. Relapse was observed in 58% of cases. For all patients, the overall survival (OS) was 89.5% at 1 year and 40.3% at 5 years. Prognostic factors influencing OS were sex ($p = 0.037$), resection margins ($p = 0.02$), recurrence ($p = 0.042$), and radiotherapy ($p = 0.023$). In multivariate analysis, radiotherapy ($p = 0.031$) and histological subtype ($p = 0.028$) were independent factors influencing OS and disease-free survival (DFS) respectively.

Conclusion: We showed that the treatment of RPSs relies on surgery with complete resection. Other factors, such as radiotherapy and the occurrence of relapse, also have an impact on OS. To facilitate surgery and to obtain negative resection margins, preoperative radiotherapy is indicated in selected patients with a high risk of relapse. Further prospective trials are warranted to select optimal therapies with less toxicity and better efficacy in reducing recurrences, mainly at a local level.

Keywords: Liposarcoma; Prognosis; Resection; Retroperitoneal sarcoma; Survival

Introduction

Soft tissue sarcomas (STSs) represent a heterogeneous group of rare mesenchymal tumors that account for less than 1% of all solid cancers in adults. STSs arising from the peritoneal cavity are referred to as retroperitoneal sarcomas (RPSs). RPSs comprise approximately 12−15% of all STSs, with an annual incidence of 5−6 cases/100,000 inhabitants.[1] The etiopathogenesis of STSs is poorly understood, although some factors may be associated with the development of STSs in less than 10% of cases, including genetic factors such as neurofibromatosis type 1, environmental factors, viral infections and irradiation.[2] Due to their deep location in the retroperitoneum, RPSs are characterized by a propensity to develop locally until they attain significant dimensions before manifesting clinical signs and symptoms. Because of the deep location, the size of the tumor at diagnosis, and the presence of adjacent vital organs (such as the pancreas, duodenum and aorta), the treatment of RPSs (surgery/radiotherapy) is complex and challenging. Surgery with microscopically negative margins remains the cornerstone of treatment for RPSs. Nevertheless, even with this approach, these tumors present a dismal prognosis, with a 36−58% 5-year survival. A high rate of local recurrence is observed; this is the main cause of death.[3] To improve outcomes, more aggressive surgeries and novel advanced techniques of radiotherapy have been developed and discussed in many studies. Furthermore, the determination of the specific prognostic factors influencing survival is paramount if we are to ensure better outcomes. Owing to the rarity of RPS, this study was conducted to better understand the particularities of this disease. We aimed to define the demographic characteristics of patients with RPSs treated in our institution. In addition, we focused on the different therapeutic approaches used in the management of RPSs and the identification of the most important prognostic factors in terms of recurrence-free and overall survival.

Materials and Methods

From 1999 to 2016, we retrospectively analyzed data from patients treated for RPS in the Department of Medical Oncology at the Habib Bourguiba University Hospital in Sfax. Patients with gastrointestinal stromal tumors, germinal tumors, lymphoma, or bone tumors were excluded. We collected a range of data from patient medical records. Demographic data included age, sex, symptoms, tumor size, grade and histological type. The confirmation of diagnosis was based on anatomopathological analysis. The main treatment involved surgery. Based on the decision made by the multidisciplinary board, radiation therapy or chemotherapy were indicated as complementary treatments. Surgical resection was considered as complete if there was no residual tumor (R0), and incomplete in the presence of microscopic (R1) or macroscopic residual tumor (R2). The tumor grade was determined according to FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer) criteria, which consider tumor differentiation, mitotic count and the presence of necrosis. Statistical analyses were conducted using SPSS software. Survival was calculated from the time of histological diagnosis to the last follow-up or death. We used the Kaplan−Meier method to generate a survival curve and studied the influence of different factors on survival using the log-rank test. A p-value <0.05 was considered significant. The independent prognostic value of these factors were analyzed with the Cox proportional hazard model.

Results

A total of 19 patients were included. The median age was 49 years (a range of 18−83 years); 68.4% of the patients were female. Patients were consulted after a mean symptom duration of 5.7 months (range: 1−24 months). The commonest symptoms included abdominal pain (88%), urinary symptoms (21%) and a palpable abdominal mass (31%). One patient presented with neurological symptoms related to spinal cord compression. A tumor was incidentally discovered in one patient. In 84% of cases, physical examination revealed an abdominal mass. Abdominal ultrasound was performed in 13 cases, while computed tomography was indicated in 16 patients (84%). None of the patients presented with metastatic disease at the time of diagnosis. The tumor was greater than 5 cm in 94.7% of cases and the median tumor size was 15 cm (range: 4−30cm). Histological diagnosis was obtained either after undergoing surgical biopsy or scan-guided biopsy (21%), or after surgical resection (79%). Complete resection was observed in 5 cases (26.3%).

Table 1: Summary of patient characteristics.

Case	Age (yr)	Sex	Time to consult (month)	symptoms	Histology	Tumor size (cm)	FNCLCC grade	Surgery	Resection (R0/R1/ unresectable)	Neoadjuvant treatment	Adjuvant treatment	Recurrence/ Type of relapse	Time to relapse (months)	Site of metastasis	Treatment of relapse
1	83	male	2	Pain Abdominal mass	Liposarcoma	11	I	Yes	R0	–	–	–			
2	54	Female	5	Pain	Liposarcoma	18	III	Yes	R1	–	Chemotherapy Radiotherapy	Yes local	27	–	No
3	78	Male	6	Pain Constipation	Liposarcoma	12	II	Yes	R0	–	–	–			
4	56	Male	6	Pain	Liposarcoma	22	–	Yes	R2	–	Palliative chemotherapy	Local progression	9		
5	61	Male	2	Pain	Liposarcoma	20	–	Yes	R0	–	Chemotherapy Radiotherapy	Yes Local + distant	7	Liver Kidney	No
6	50	Female	1	–	Liposarcoma	17	I	Yes	R1	–	–	Yes Local	3	–	Complete resection + adjuvant radiotherapy
7	46	Female	9	Pain	Liposarcoma	18	III	Yes	R1	–	–	Yes Local	2	–	No
8	32	Male	7	Mass Urinary symptoms	Liposarcoma	30	III	Yes	R2	–	Palliative chemotherapy				
9	49	Male	6	Pain Weight loss	Leimyosarcoma	6,5	I	No	Unresectable	–		–			
10	47	Female	4	Pain Weight loss	Leimyosarcoma	11	III	No	Unresectable	Chemotherapy then surgery (R1)	Radiotherapy	Yes Local + distant	2	Lung Liver	Chemotherapy
11	59	Female	8	Pain	Leimyosarcoma	4	I	Yes	R0	–	–	–			
12	29	Female	6	Pain	Leimyosarcoma	15	III	Yes	R2	–	Chemotherapy with complete remission	Yes Local	2		Chemotherapy
13	58	Female	1	Renal failure	Leimyosarcoma	20	I	Yes	R1	–		Yes Local	2		Surgery (R1) Radiotherapy Chemotherapy
14	26	Female-	12	Pain	Neurofibrosarcoma	5,5	–	Yes	R2	–	Palliative Chemotherapy With local progression	–			
15	19	Female	2	Pain Weight loss	Extraosseous Ewing sarcoma	17	–	Yes	R2			Yes Local + distant	2	Pleural Lung	
16	18	Female	4	Weakness in the legs with loss of sensation	Extraosseous Ewing sarcoma	12	–	Yes	R0	–	Chemotherapy Radiotherapy	Yes distant	12	Bone	Chemotherapy
17	18	Female	1	Pain Mass	Extraosseous Ewing sarcoma	12	–	Yes	R2	–	Chemotherapy Radiotherapy	–			
18	57	Female	24	Pain Urinary symptoms	Synovialosarcoma	9	III	Yes	R2	–	Chemotherapy	Yes Local + distant	3	Pleural	Chemotherapy
19	65	Female	3	Pain	Liposarcoma	20	II	No	Unresectable	Chemotherapy		Progression			Chemotherapy

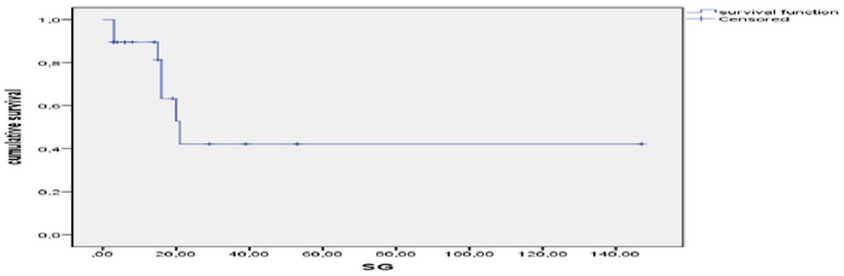

Figure 1: Overall survival curve.

Multi-visceral resection was needed in 4 patients (21%). Following an initial incomplete resection, three patients underwent a second round of surgery. The most common histological subtypes were liposarcoma (47.4%) and leiomyosarcoma (26.3%). Other subtypes were evident, including extraosseous Ewing sarcoma (3 cases) and synovial sarcoma (1 case). The tumor grade was identified in 13 patients. Eight patients had a high-grade tumor (G2 = 2 or G3 = 6). None of the patients received preoperative radiotherapy, although this was delivered in an adjuvant situation in 5 patients (26.3%) with a high risk of local relapse (range: 45–64 Gy). Chemotherapy was administered as a neoadjuvant treatment in two patients with non-resectable tumors. Chemotherapy was indicated in an adjuvant situation (31%) and as a palliative treatment in locally advanced or metastatic disease (42%). Chemotherapy was based especially on anthracyclines (doxorubicin) and alkylating agent (ifosfamide). Other agents were administered, including dacarbazine, etoposide, cisplatin, gemcitabine, and docetaxel. The most observed toxicities were hematological (58%) and digestive (53%). No toxic deaths were reported. During follow-up, seven patients were found to be disease

Table 2: Prognostic factors for overall and event-free survival.

Variables	*Patients n = 21*	Overall survival		Event free survival	
		P (univariate analysis)	P (multivariate analysis)	P (univariate analysis)	P (multivariate analysis)
Sex					
Male	6	0.037	0.74	0.54	0.31
Female	13				
Age					
<30 years	6	0.96	0.88	0.27	0.36
>30 years	13				
Time between the onset of symptoms and consultation					
<6 months	15	0.059	0.27	0.65	0.27
>6 months	4				
Tumor size (cm)					
<5	18	0.73	0.99	0.49	0.9
>5	1				
Histological type					
Liposarcoma	9	0.76	0.96	**0.005**	**0.028**
Non liposarcoma	10				
Grade FNCLCC					
G1	5	0.41	0.27	0.2	0.16
G2/3	8				
Unknown	6				
Type of resection					
Complete (R0)	5	**0.02**	0.61	0.06	0.19
Incomplete (R1, R2)	13				
Unresectable	1				
Radiotherapy					
Yes	7	**0.023**	**0.031**	0.44	0.14
No	12				
Chemotherapy					
Yes	12	0.307	0.47	0.32	0.09
No	7				
Relapse					
Yes	12	**0.042**	0.93	**0.007**	0.95
No	7				

free. Two patients who received neoadjuvant chemotherapy for a non-resectable tumor developed disease progression and were treated with second line chemotherapy. Recurrence was observed in 10 cases (58%) after a mean duration of 6 months (range: 2–27 months). Five patients had only local relapses, while four patients presented with both local and distant recurrences. The sites of metastases were mainly the lungs and liver. Furthermore, the occurrence of distant metastases to bones without local relapse was observed in one patient treated initially for an extraosseous Ewing sarcoma. Patient characteristics and different treatment modalities are summarized in Table 1. For all patients, the median overall survival (OS) was 21 months and was 89.5% and 40.3% at 1 and 5 years, respectively (Figure 1). The disease-free survival (DFS) was 28.6% at 1 year and 14.3% at 5 years, with a median of 1 month. Sex, resection margins, radiotherapy, and the occurrence of relapse were found to be prognostic factors for OS. In multivariate analysis, radiotherapy and histological subtype were found to be independent factors influencing OS and DFS, respectively (Table 2).

Discussion

RPSs are rare mesenchymal tumors, accounting for 12–15% of all STSs.[1] Many histological subtypes of RPSs may be defined according to their lineage. The most frequent histological types are liposarcoma and leiomyosarcoma; these were identified in the present study. Mendenhall et al.[4] reported that 26–57% of all RPSs were liposarcomas, followed by leiomyosarcoma (17–29%), malignant histiocytofibroma (7–17%), rhabdomyosarcoma (7%), synovial sarcoma (2%), and Ewing sarcoma (2%). The mean age of our patients was 45 years, much younger than that reported in European studies, where the median age was 54 years.[5] The distribution of the type of sarcoma varies according to age. It has been observed that leiomyosarcoma and synovial sarcoma are more common in younger patients.[6] Generally, RPSs affect both sexes equally; however, as observed in our study, some retrospective studies suggest a slight female predominance.[7] Clinical symptoms appear late in RPSs and are non-specific, thus explaining the large size of the tumor and the delay in diagnosis. In our study, the mean time between symptom onset and diagnosis was 5.7 months; this is rather long and consistent with that reported in the literature (6–24 months).[5] Abdominal pain is the most relevant symptom (88% of cases in our study). Other manifestations related to the compression of adjacent organs by the abdominal mass include constipation and urine retention. RPSs are characterized by a large tumor size that exceeds 5 cm and 10 cm in 94% and 60% of cases, respectively, as reported by Lewis et al.[3] In our patients, the tumors were greater than 5 cm in 94.7% of cases. Thus, the diagnosis of sarcoma must be suspected in the presence of any mass exceeding 5 cm. The role of imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI) is crucial in terms of RPS. CT is the most helpful and available technique and can identify, localize, and characterize tumors, rule out other differential diagnoses and facilitate planning for surgical resection. MRI is often reserved for cases of allergy to iodinated contrast agents and to assess the local extension of a tumor in patients proposed for radiotherapy. Fluorodeoxyglucose-positron emission tomography (FDG PET)/CT may be indicated in cases of suspicious lesions, but does not have a routine role.[6] In our study, CT was performed in most patients (84%). However, the final diagnosis of RPSs is based on histological examination. Tumor tissue is generally obtained by core needle biopsy guided by imaging, which presents the safest and preferred method to establish a histological diagnosis.[8] Referral to specialized centers for all patients with RPSs is highly encouraged and recommended by the European CanCer Organization (ECCO) in collaboration with the Sarcoma Patients Euronet (SPAEN), the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO). Treatment was carried out in a university hospital center for most of our patients. The management of RPSs is based on surgery; this is currently the most effective and curative treatment. The aim of surgical resection is to achieve a macroscopic complete resection; this was achieved in only 5 cases in our patient cohort. To ensure negative margins, the resection of one or more adjacent organs together with the primary tumor might be necessary. Most frequently, resected organs are the ipsilateral kidney or hemi-colon. It has been established that compartmental surgery is better than conventional surgery and therefore recommended for the management of localized or locally advanced RPSs.[9] Despite this approach, and even in the case of complete resection, the rate of local recurrences remains high in RPSs. To improve local control of the disease, the addition of radiation therapy as neoadjuvant or adjuvant treatment has been largely discussed, although its precise role and timing remains unclear. In a study published in 2006, including 2348 cases of RPSs, Porter et al.[10] reported that in general practice, radiotherapy was indicated in only 25.9% of patients but was delivered postoperatively in the majority of cases (85.5%).

The use of adjuvant radiotherapy, with doses of 35–50 Gy, has been reported to reduce local recurrences of RPSs in several retrospective studies. However, the benefit of postoperative radiotherapy is small compared to the significant toxicity.[11]

The role of preoperative radiotherapy is to minimize toxicity to adjacent organs which are displaced by the tumor mass, to reduce tumor size, thicken the tumor pseudocapsule and facilitate surgery to obtain clear margins (R0) while minimizing peritoneal seeding.[12] Pawlik et al.[13] demonstrated that complete surgical resection was possible in 75% of cases after receiving preoperative radiotherapy with an OS of 61% at 5 years. Analysis of data from 11 studies of RPSs in a recent systematic review and meta-analysis showed lower rates of local recurrences with neo-adjuvant in comparison with adjuvant radiotherapy (odds ratio [OR], 0.03; $p = 0.02$).[14]

However, the EORTC-62092: STRASS study, a randomized phase 3 study, compared preoperative radiotherapy plus surgery against surgery alone for patients with primary RPS that was operable and suitable for radiotherapy. This trial was negative, with similar outcomes in terms of abdominal recurrence-free survival and overall survival in both groups at 3 years of follow-up; serious adverse events were most frequent in the radiotherapy plus surgery group

(24% *vs* 10%).[15] Based on the NCCN guidelines, neoadjuvant radiotherapy can be considered for selected patients with RPSs who are at high risk for local relapse.[14] In the current study, none of the patients received preoperative radiotherapy although this was delivered postoperatively in 26.3% of patients, especially in cases of incomplete resection, a large tumor size and high grade tumors.

Because of the rarity of RPSs, data on chemotherapy and biological therapy are usually extrapolated from studies on extremity sarcomas. The type of systemic therapy used is guided by the histological subtype of the RPSs. Some subtypes, such as myxoid liposarcoma and synovial sarcoma, are the most chemosensitive types, followed by pleomorphic liposarcoma and leiomyosarcoma; dedifferentiated liposarcoma is chemoresistant.[16] Anthracyclines and alkylating agents are the most effective and commonly used drugs in RPSs. The rationale for the use of perioperative chemotherapy is based on concepts such as preoperative tumor cytoreduction, the sterilization of micrometastases and the evaluation of tumor chemosensitivity.[17] Neoadjuvant chemotherapy was administered to two of our patients with unresectable tumors. Adjuvant chemotherapy is not considered a standard approach for RPS. Most of the trials involving adjuvant chemotherapy in STS implicate treatment of the extremities or trunk wall primaries. It is still unclear how exactly their results can be extrapolated to retroperitoneal tumors.[11] In our study, 31% of patients received chemotherapy in an adjuvant situation in the case of positive resection margins and a high-grade tumor. As reported in some studies, the use of systemic therapy in advanced and/or metastatic RPSs may improve overall survival.[17] This malignancy is associated with a poor prognosis. Our results in terms of overall survival are similar to those reported in the literature (66% and 39% at 1 and 5 years, respectively), but in terms of DFS, our results are inferior. This might be related to the high rate of incomplete resection in our study (68.5%). Prognostic factors influencing the OS and DFS have been evaluated in significant depth. An age older than 60 years has been reported as a poor prognostic factor, but this did not influence OS in our cohort of patients ($p = 0.96$). In our patients, the OS was better in females ($p = 0.037$). This was concordant with results reported by Toulmonde et al.[18] ($p < 0.001$) and Abdelfatah et al.[19] ($p = 0.012$). Lewis et al.[3] reported that histological type is a prognostic factor of DFS with better outcomes in liposarcoma. In our study, patients with liposarcoma had a better DFS at 1 year ($p = 0.05$). However, by applying multivariate analysis, Gronchi et al. did not demonstrate a prognostic impact of histological subtype on OS and DFS.[20] In RPS, tumor grade is a major independent prognostic factor. In contrast with many studies, grade was not associated with worse outcomes in our patients ($p = 0.41$) probably because of the small number of patients and the frequency of ungraded histological types (31.6%). Gronchi et al. found that incomplete resection (R1/R2) resulted in poor survival ($p = 0.01$) and a high rate of recurrence ($p = 0.001$).[21] We also observed this in the present study with a better survival at 5 years in patients with complete resection (100% vs. 50% [R1] and 20% [R2]). In RPS, death is often related to local recurrences. The rates of local or peritoneal recurrences range from 44% to 85%.[22] In the current study, 10 patients (58%) experienced a relapse; in 5 cases, this was local. Positive resection margins were observed in all 5 cases. The treatment of recurrence is based on surgery and must be discussed by a multidisciplinary board. In our study, two patients with local relapse underwent surgery followed by radiation therapy. The occurrence of distant metastases was observed, especially in cases of non-liposarcoma types and high-grade tumors. In our study, 2 patients with grade III leiomyosarcoma had distant relapses.

Conclusion

Our study has some limitations that need to be considered. For example, our study featured a retrospective design and involved a small number of patients. Compared to the literature, we found that RPSs were present in younger patients. Our results were similar in terms of OS but inferior regarding DFS; this can be explained by the frequency of incomplete resection in patients treated with surgery. The optimal treatment for patients with RPS relies on radical surgery with complete resection; this was correlated to survival in our present study. However, achieving this complete resection is challenging in many cases. Therefore, the development of other strategies, such as preoperative radiotherapy, has an important role in facilitating surgery and improving results. In our study, radiotherapy was delivered to patients with incomplete resection or high-grade tumors and was correlated with overall survival, thus implying a benefit but lacking evidence. Recurrence is recognized as a prognostic factor and the optimal treatment for this has yet to be fully elucidated. Further studies are now warranted to select optimal therapies with less toxicity and better efficacy in reducing recurrences, mainly at the local level.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committees of Habib Bourguiba and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors contributions

JF, ML and DS conceived and designed the study, conducted the research, provided research materials, and collected and organized data. MF and RBH analyzed and

interpreted the data. MHS, JD and AK wrote the initial and final drafts of the article, and provided logistical support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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