Challenges in the Surgical Treatment of Retroperitoneal Sarcomas

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Abstract The objective of this study is to assess long-term prognosis and patterns of failure in patients with retroperitoneal sarcoma who underwent surgery with curative intent at a single institution. We also provide a thorough review of the literature including several series and widely variable data regarding local and distant failure. During a 25-year period (1988–2013), 45 consecutive patients who underwent surgery for retroperitoneal sarcoma at a single referral center were reviewed retrospectively. We recorded and analyzed the presenting symptoms, type of surgical excision, and the 5-year survival rate as well as the local recurrence rate of patients with complete tumor resection. Overall survival is significantly diminished in patients in whom resection margins are not adequate. In our series, 5-year recurrence rate for patients with complete and incomplete resection of the tumor was 30.76 and 68.42 %, respectively. The 5-year survival rate was 51.12 %, and the 5-year survival rate according to type of resection was 76.93 % for complete and 15.79 % for incomplete resections. Local recurrence after first surgery and high-grade malignancy are associated with poor survival. The role of radiation therapy and chemotherapy in the treatment of retroperitoneal sarcoma (RPS) should be investigated further. Complete en bloc resection of the tumor mass and adjacent structures is the single most important factor that improves survival.

Keywords Retroperitoneal sarcoma · Surgical excision · Adjuvant therapy · Recurrence

Introduction

Retroperitoneal sarcomas (RPSs) are uncommon neoplasms that are usually locally advanced when diagnosed. They account for less than 1 % of all malignancies [1]. Sarcomas are believed to develop from mesenchymal stem cells residing in muscle, fat, and connective tissues. They remain occult for long periods and grow relatively large due to the abdominal cavity's remarkable ability to accommodate these slowly expanding masses with a paucity of attendant symptoms [2]. These tumors have a well-earned reputation for local recurrence [3–5]. The prognosis of patients with RPS is generally poor, especially when assessed over long term [6–9]. Reported 5-year survival rates range between 12 and 70 % [10].

Background

Complete surgical resection is the treatment of choice, but it is difficult due to the anatomical location, late presentation, and frequent invasion of adjacent retroperitoneal structures. The contribution of adjuvant chemotherapy to the treatment of adult patients with RPS remains questionable, whereas radiation therapy is either unfeasible or affected strongly by anatomic constraints. Surgery alone is curative in a relatively small number of patients.

Available studies vary widely with regard to estimate of cured or long-term survivors, most likely depending on strong variation in the referral pattern of the various institutions. According to these studies [1, 6], high histological grade,

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unresectable primary tumor, and incomplete resection are associated with a poor outcome.

The aim of this study is to analyze disease-specific survival and disease-free survival in a cohort of prospectively followed patients with RPS managed at a single institution. In particular, we analyzed the correlation of tumor biology and surgical treatment with subsequent local recurrence, metastasis, and disease-specific survival. The focus is to determine the role of surgical resection in the management of primary and locally recurrent disease.

Materials and Methods

During a 25-year period (1988–2013), we managed 45 patients with retroperitoneal sarcomas. All the patients referred at the 2nd Department of Propedeutic Surgery of the University of Athens, Medical School. The study protocol was conformed to the guidelines of the 1975 Declaration of Helsinki.

Inclusion criteria were (1) age ≥ 18 years old, (2) patients who reported to have a primary sarcoma of the retroperitoneum, and (3) patients that underwent treatment only at our center.

Patient, tumor, and treatment variables were correlated with survival endpoints. Patient variables analyzed included age at diagnosis and sex. Tumor variables analyzed included size (<10 or ≥ 10 cm), histologic grade (low or high), and histologic subtype. Histologic grade was divided into low or high, distinct from other aspects of intermediate transition. Treatment variables analyzed included complete versus incomplete resection and microscopic margins.

Adjuvant radiation or chemotherapy was not prospectively randomized but included both patients prospectively treated in trials and those given standard of care based on prognosis, the inclusion of these variables in any of the analyses would confound the effects of other factors. Therefore, although we report these treatment data, we have chosen not to include them in any of the analyses. Patients' demographics are summarized in Table 1.

The male/female ratio was 20:25 and the age ranged from 45 to 72 years (mean age, 61 years). Preoperative evaluation was performed in all cases. A thorough medical history and physical examination were the first steps of the preoperative evaluation. The workup for metastatic disease included chest radiography and/or computed tomography (CT scan). A thorough follow-up was done for all patients.

The surgical treatment aimed at achieving complete removal of the tumor en bloc with a safety margin of adjacent normal tissue in all directions. The margin of normal tissue around the tumor mass, as identified by the pathologist, determined the classification of the procedure

Table 1 Patients' demographics

Variable	Male	Female	Total
Patients	<i>n</i> =20	<i>n</i> =25	45
Age (yrs $\pm$ SD)	59.7 $\pm$ 8.04	59.08 $\pm$ 8.42	59.3 $\pm$ 8.16
Follow-up (m)	49.2 $\pm$ 27.5	46.88 $\pm$ 24.7	47.9 $\pm$ 25.7
Symptoms			
Ascites	12	17	29
Discomfort	6	9	15
Obstruction	1	3	4
Neurologic	–	3	3

yrs years, SD standard deviation, m months, discomfort abdominal discomfort, obstruction bowel obstruction

as wide, marginal, or intralesional. The excision was considered wide if negative margins were histological confirmed. Marginal resection was defined when the complete macroscopic removal of the tumor mass had histological confirmed positive surgical margins. The excision was considered intralesional if there was macroscopic residual disease.

The position of the patients and surgical incision were dependent on tumor location. For RPS of the upper quadrants of the abdomen, a thoracoabdominal incision was performed, with the patient in lateral position. For RPS of the pelvis or in the midline, the patient was placed in a supine position and a long midline incision was made with lateral extension when necessary. En bloc resection of the tumor with adjacent structures was performed so as to obtain free margins.

In 35 patients, at least one organ was resected completely or partially. The most frequent organ resected in our series was the ureter (15 patients), followed by the bowel (11 patients), the adrenal gland (7 patients), and other organs (4 patients). The mean number of organs resected per operation was 1, and maximum number of organs resected per operation was 2.

Local recurrence was defined as recurrent tumor in the retroperitoneum or abdominal cavity. Distant recurrence was defined as the disease in organs or outside abdominal cavity.

Postoperatively, the decision to administer adjuvant radiotherapy or chemotherapy was taken by the operating surgeon and the oncologist when they believed that there was a high risk of local recurrence based on clinical grounds. A problem associated with adjuvant radiotherapy is that the dose is limited by the tolerance of the surrounding normal tissues, primarily the small bowel, to 40–50 Gy over 5 weeks. Anthracycline-based regimens were used as adjuvant chemotherapy for patients with disseminated disease and high-grade sarcomas.

We recorded the presenting symptoms, type of surgical excision, and the 5-year survival rate as well as the local recurrence rate of patients with complete tumor resection.

Results

Liposarcoma was the main histotype (14 patients), followed by leiomyosarcoma (13 patients), fibrosarcoma (6 patients), neurogenic sarcoma (2 patients), undifferentiated (9 patients), and angiosarcomas (1 patient). Table 2 analyzes, patient-by-patient, tumor characteristics.

According to the American Joint Committee staging system for soft-tissue sarcomas [11], the patients, in our series, were classified as follows: 8 patients (17.78 %) were classified

as stage I, 20 patients (44.44 %) were classified as stage II, 10 patients (22.22 %) were classified as stage III, and 7 patients (15.56 %) were classified as stage IV. Five patients had regional lymph node involvement and four patients showed distant metastases at presentation, in liver (one patient) and lung (three patients), respectively.

Surgical procedures were tolerated well by all the patients. Hospital stay ranged from 10 to 15 days for the inpatients, including those who had staged operations or any complication necessitating a second operation.

Presenting symptoms included a non-tender palpable mass in 29 patients, vague abdominal discomfort in 15 patients, obstructive gastrointestinal symptoms in 9 patients, 3 patients with non-malignant serous ascites due to external portal vein obstruction, and 4 patients who had distal neurologic symptoms due to stretch or compress of the pelvic or lumbar nerves from the tumor mass. Gastrointestinal symptoms were of a partially obstructive nature due to displacement or direct invasion by the expanding mass. In our series, all patients appeared with tumors measuring more than 10 cm in their greatest diameter.

Antibiotic prophylaxis was administered according to the preference of the attending surgeon. Single broad-spectrum antibiotic regimens were used in the majority of cases.

The excised tumor mass was sent to the pathologist in order to examine the surgical margins. Twenty-six patients underwent complete tumor resection with histological confirmed negative margins. Eight patients underwent complete macroscopic removal of the tumor mass with histological confirmed positive surgical margins somewhere. Six patients underwent partial resection of the tumor mass and five patients underwent biopsy only.

Complications were divided into two groups: (1) early complications, which occurred during the first month. We found six patients with ileus, two patients with postoperative hemorrhage, and eight patients with wound infection. (2) Late complications, which occurred after the first month. We found local recurrence in 8 out of the 26 patients with complete resection of the tumor and in 13 out of the 19 patients with incomplete resection of the tumor. We found multiple recurrences in 4 out of 19 patients with incomplete resection of the tumor (liver, 1 patient; lung, 3 patients). Twenty-two patients died within the first 5 postoperative years; 6 out of these patients underwent complete resection of the tumor and 16 out of these patients incomplete resection of the tumor.

Thirty-three patients underwent adjuvant radiotherapy or chemotherapy. Out of them, radiation therapy was given to 6 patients and chemotherapy to 27 patients. Adjuvant chemotherapy was mostly given to patients with high-grade sarcomas. Chemotherapy was given to 15 patients with complete tumor resection and in 12 patients with incomplete tumor resection. Radiation therapy was given to six patients with incomplete tumor resection.

Table 2 Patient-by-patient analysis of tumor characteristics

<i>n</i>	<i>G</i>	<i>A</i>	<i>T</i>	<i>S</i>	<i>OR</i>	<i>Gr</i>
1	M	52	Liposarcoma	≥10	Ureter, kidney	High
2	F	57	Leiomyosarcoma	<10	Bowel	Low
3	F	59	Undifferentiated	<10	Spleen	High
4	F	68	Liposarcoma	<10	Bowel	Low
5	F	66	Leiomyosarcoma	<10	Adrenal gland	High
6	M	69	Fibrosarcoma	≥10	Ureter	Low
7	M	72	Angiosarcoma	<10	Bowel	Low
8	M	46	Undifferentiated	<10	Bladder	High
9	F	49	Neurogenic sarcoma	<10	Ureter	Low
10	M	51	Liposarcoma	≥10	Ureter, kidney	High
11	F	58	Fibrosarcoma	<10	Bowel	Low
12	M	66	Leiomyosarcoma	<10	Adrenal gland	Low
13	M	49	Liposarcoma	≥10	Ureter	High
14	M	50	Liposarcoma	<10	Bowel	High
15	F	65	Leiomyosarcoma	<10	Adrenal gland	Low
16	M	69	Undifferentiated	<10	Ureter	High
17	M	71	Liposarcoma	≥10	Bowel	High
18	M	64	Neurogenic sarcoma	<10	Adrenal gland	Low
19	F	53	Fibrosarcoma	<10	Ureter	Low
20	F	58	Liposarcoma	<10	Adrenal gland	Low
21	M	65	Undifferentiated	≥10	Ureter	High
22	F	71	Leiomyosarcoma	<10	Bowel	Low
23	M	48	Undifferentiated	<10	Ureter	High
24	F	45	Liposarcoma	<10	Ureter	Low
25	M	72	Leiomyosarcoma	≥10	Bowel	High
26	M	65	Fibrosarcoma	<10	Bowel	Low
27	F	56	Liposarcoma	<10	Ureter	High
28	F	54	Fibrosarcoma	<10	Adrenal gland	Low
29	F	48	Liposarcoma	<10	Ureter	Low
30	M	71	Leiomyosarcoma	<10	Adrenal gland	High
31	F	66	Leiomyosarcoma	<10	Ureter	Low
32	F	49	Liposarcoma	≥10	Bowel	High
33	M	50	Undifferentiated	<10	Ureter	High
34	F	53	Leiomyosarcoma	<10	Bowel	Low
35	M	59	Liposarcoma	<10	Ureter	Low

n, identification number; *G*, gender (male/female); *A*, age (years); *T*, primary tumor; *S*, tumor size; +, max diameter over 10 cm; *OR*, organs resected; *Gr*, histological grade

Patients were examined at least three times in the first postoperative year and two times in the second postoperative year, during routine follow-up. The survival was calculated from the month of the first surgical treatment at our center to the last follow-up or death. Local recurrences were treated with debulking or complete resection where feasible and possible. The analysis of these data was not made since the 5-year follow-up was not reached in many patients as well as it is out of the scope of current study.

Discussion

Retroperitoneal sarcoma is not a single disease but a collection of several different types of neoplasms related only by a common histogenetic origin [3]. The combination of infrequent occurrence and varied pathologic features constitute these tumors a challenge for the oncologist. Unfortunately, marginal resection is achieved in the majority of patients who undergo macroscopic total resection with a subsequent high likelihood of local recurrence.

It is generally recognized that the major factor influencing the survival outcome is the complete resection of the tumor mass [2, 5, 11]. The rate of complete resection has varied in the literature from 38 [10] to 74 % [12], with other reports falling in between [3–5, 13], while the average complete resectability rate in a collective review was 53 % [2]. Ferrario et al. [8] believe that the low resectability rate in the literature is due to the fact that the majority of patients with RPS are operated on in a supine position through a midline abdominal incision that does not take advantage of gravity for patients with upper quadrant or flank tumors.

After complete resection of the tumor, the most important biological factor to determine survival has been the grade of the RPS [2, 3, 14]. Grade is depending on the number of mitoses, the degree of cellular and nuclear atypia, and the presence and extent of necrosis [2, 3, 15]. According to the American Joint Committee staging system for soft-tissue sarcomas [2, 3, 16], the grade of the tumor directly determines the stage of the disease. Tumor size is the second determinant of the stage.

Our study confirms previous reports [3, 9, 14], which indicate that the two most important factors for survival in RPS are the completeness of the tumor resection and the histological grade of the tumor. Thus, aggressive surgical management of these tumors is almost always the mainstay for achieving complete resection so as to optimize survival [2, 17]. Gronchi et al. [18] reported that liposarcomas were characterized mainly by a high local failure rate, whereas distant metastases constituted the main cause of failure in patients with non-liposarcomas.

Prevention of local recurrence of RPS is the most important goal of the treatment in surgery. The main factors determining tumor resectability are size and the anatomical location of the tumor. The surgeon who performs the first definite resection

must obtain the widest possible excision, with little hesitation to excise and remove adjacent organs in order to achieve complete en bloc removal of the tumor mass [19]. In our series, 5-year recurrence rate for patients with complete and incomplete resection of the tumor was 30.76 and 68.42 %, respectively. Our results are comparable to the recurrence rate of similar patients in major centers. Overall survival is significantly diminished in patients in whom resection margins are not adequate. The 5-year survival rate was 51.12 %, and the 5-year survival rate according to type of resection was 76.93 % for complete and 15.79 % for incomplete resections. The low 5-year survival rate for patients with incomplete resection of the tumor was due to the large dimensions of the tumor and the high grade of the tumor. In addition, the application of prophylactic lymph node dissection has no sense in the management of RPS [8–10].

Although the effectiveness of radiation therapy has been demonstrated for patients with soft-tissue sarcomas of the limb [20], its effectiveness is limited in patients with RPS by the difficulty in delivering adequate doses to the retroperitoneum and the abdomen [17]. There are ongoing trials of preoperative radiation associated with an intraoperative or a postoperative boost [21, 22]. Patients who receive preoperative radiation therapy have a modest increased risk of delayed wound healing, depending on the dose of radiation. On the other hand, small bowel toxicity is likely to be less pronounced with preoperative radiation therapy compared with postoperative radiation therapy. This is due to the fact that the tumor mass displaces much of the small bowel out of the radiation therapy field. Moreover, it is necessary to evaluate renal function prior to radiation therapy in order to avoid a renal complication. In our series, radiation therapy was always performed postoperatively and proved to be of little value in increasing the survival rate.

Systemic chemotherapy is recommended for those tumors with a significant risk of distant metastases. Increasingly, neoadjuvant chemotherapy is being used to determine responsiveness to chemotherapy, which can help physicians select patients who may benefit from systemic postoperative therapy [23]. In our series, the 5-year survival rate of patients who had received adjuvant chemotherapy was 44.45 %. We believe that adjuvant chemotherapy may be useful in the treatment of patients with high-grade RPS [24, 25].

Conclusions

The results of the current series demonstrate that local recurrence after first surgery and high-grade malignancy are associated with poor survival. The role of radiation therapy and chemotherapy in the treatment of RPS should be investigated further. Complete en bloc resection of the tumor mass and adjacent structures is the single most important factor that improves survival.

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