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Outcomes of Surgery in Elderly Patients with a Retroperitoneal Soft Tissue Sarcoma

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Abstract

Aim of this Study: To evaluate short and long term results after curative surgery for a retroperitoneal sarcoma (RPS) in elderly patients.

Methods: We retrospectively analyzed data of all patients operated in our single tertiary care center for a non-metastatic RPS and identified patients older than 70.

Results: Among 304 patients with a RPS treated between 1994 and 2015, 62 (20%) were older than 70 (median age 75 years, range: 70-85). The median tumor size was 26 cm (range: 11-46). 46 patients (74%) had mass-related symptoms at the time of diagnosis. The most frequent histological subtype was liposarcoma (76%). 22 patients (35%) had a perioperative radiotherapy and/or chemotherapy. 58 patients (94%) had macroscopically complete resection. The postoperative mortality was 6% and severe morbidity (including deceased patients) was 39%. A reoperation was required for 11 patients (18%). After a median follow-up of 20 months (range: 0-120), the 5-year Overall Survival (OS) rate was 90% (IC95%: 79%-100%) and the median OS was not reached. Cancer specific death rate was 86%. No prognostic factor for disease specific survival was detected. The 5-years disease free survival DFS rate was 52% (IC 95%: 33%-84%) and the 5-years loco-regional recurrence-free survival (LR-RFS) rate was 52% (IC 95%: 33%-84%). Median DFS was 94 months (range: 35-139). Reoperation after inappropriate surgery and postoperative morbidity were independent predictive factors of loco-regional relapse. No predictive factors of distant metastasis were found.

Conclusions: Curative surgery is feasible in selected elderly patients with an acceptable morbidity and with potential action on symptoms. It enables a prolonged survival. Future studies should focus on selection process.

Keywords: Soft tissue sarcoma; Surgery; Elderly; Cancer; Retroperitoneal sarcoma

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Introduction

Soft Tissue Sarcomas (STS) account for 2% of all adult cancers [1]. With an estimated incidence of 59 per million and per year, approximately 30,000 new cases are diagnosed yearly in Europe, 11,900 in the United States and 2000 in Japan [1-3]. Fifteen percent of all STS are located in the retro-peritoneal space [1-2]. Surgery is the reference treatment for non-metastatic retro-peritoneal soft tissue sarcomas (RPS). The extent of surgery is still debated. An international multi-centric series on 1007 patients have recently shown better results, attributed partially to a more aggressive surgical approach consisting in a systematic in-bloc resection with adjacent viscera even when not overtly involved [4]. With this approach, 5 years overall survival (OS) was 67%, and the median survival 116 months [4]. Nevertheless, few data exist on the potentially increased morbidity associated with multivisceral resection, especially in elderly patients. The aim of this study was to evaluate short and long term results after excision of RPS in patients aged over 70 years, to determine if surgery should be proposed to these patients.

Methods

Patient's selection

We retrospectively analyzed all patients operated for a primary RPS in our single tertiary care

Table 1: Demographics and perioperative characteristics.

	All patients		<70 years		>70 years		P
	n	%	n	%	n	%	
Total	304	100	242	80	62	20	
Medianage (years) [range]	**57 [24 - 85]**		**52 [24 - 69]**		**75 [70 - 85]**		
Sex							0.8
Female	150	49	119	49	32	52	
Male	154	51	123	51	30	48	
Multifocality							NS
Yes	4	1	3	1	1	2	
No	300	99	239	99	61	98	
First tumorresection							
Yes	248	82	193	80	54	87	
No	56	18	49	20	8	13	<0.01
Chemotherapy							
Yes	74	24	67	28	7	11	
No	230	76	175	72	55	89	
Radiotherapy							<0.01
Yes	131	43	115	48	15	24	
No	173	57	127	52	47	76	
FNCLCC grade							0.4
I	130	43	109	45	21	34	
II	92	30	70	29	22	35	
III	74	27	59	24	15	24	
N/A	3	1	2	1	3	9	
Median tumor size (cm) [range]	**24 [1-60]**		**24 [2 - 60]**		**26cm [11 - 46]**		NS
Histologicsubtype							
LMS	31	10	25	10	6	10	
Undiff-S	89	29	78	32	11	18	
DD-lipoS	44	14	28	12	16	26	
WD-lipoS	94	31	74	31	20	32	
MPNST	10	3	10	4	0	0	
UPS	8	3	5	2	3	5	
Other	21	7	17	7	4	6	
Extent of resection							
Complete	292	96	234	97	58	94	
Incomplete	5	2	3	1	2	3	
No resection	7	2	5	2	2	3	
Resectedorgans							NS
None	25	8	21	9	4	6	
One organ	40	13	35	14	5	8	
More than 1 organ	239	79	187	77	52	84	
Vascularresection							NS
Yes	32	11	30	12	2	3	
No	272	89	212	88	60	97	

N/A: Not Evaluable; LMS: Leiomyosarcoma; Undiff-S: Undifferentiated Liposarcoma; DD-lipoS: Dedifferentiated Liposarcoma; WD-lipoS: Well-Differentiated Liposarcoma; MPNST: Malignant Peripheral Nerve Sheath Tumor; UPS: Undifferentiated Pleomorphic Sarcoma

center between November 1994 and October 2015 to identify patients older than 70 years. Inclusion criteria were (i) data available on initial treatment and follow-up and (ii) no concomitant uncontrolled other cancer. We excluded patients with non-sarcoma pathology, as well as

patients with solitary fibrous tumors, or with uncertain malignancy. Patient's files were retrospectively analyzed.

Variables analyzed

The analyzed variables were preoperative data (gender, age, tumor location, size, symptoms), peroperative data (date of surgery, resection performed, mortality and postoperative morbidity, histology, microscopic margins, perioperative radiotherapy and/or chemotherapy) and long-term data (overall survival, disease-free survival, type of recurrence, death).

Preoperative work-up

All patients with RPS scheduled for surgery had a clinical evaluation examination, a preoperative thoraco-abdomino-pelvic CT-scanner and an abdomino-pelvic MRI when required on the surgeon's advice. Patients with metastatic disease on imaging or with poor general status (i.e. ECOG 3-4) were considered unfit for surgery. All tumors had a preoperative needle core biopsy with a 14- or 16-gauge using an imaging-guided coaxial technique. The loco-regional contra-indications for surgery were based on technical criteria reported by the EORTC-STBSG in 2012 [5].

Surgical technique

Surgery was performed according to the 2012 consensus statements from the EORTC-STBSG European and North American expert sarcoma surgeons [5]. The quality of the tumor resection was defined according to the UICC criteria. Tumor rupture during surgery and incomplete resection were recorded.

Postoperative morbidity

Surgical complications during the hospitalization were retrospectively recorded and graded according to the Dindo/Clavien classification [6]. A post-operative complication was considered significant when the grade was greater than 2.

Pathological staging

All surgical specimens were analyzed and retrospectively converted according to the 2012 WHO classification, with a further molecular analysis whenever necessary. The pathology analysis included the tumor grading using the FNCLCC classification and the UICC TNM staging system [7-9].

Long term follow-up

Patients were followed with clinical examination and abdomino-pelvic CT-scanner twice a year for 5 years and yearly afterwards. Recurrences were diagnosed either on a clinical or radiological basis, without required histological proofs, and systematically confirmed with a multidisciplinary team decision.

Statistics

We calculated Overall survival (OS), time to local recurrence, and time to metastasis using the Kaplan-Meier method and computed confidence intervals with Rothman's method. OS was computed from the date of primary tumor resection to the date of death or the last follow-up. Patients with postoperative death were excluded from survival analysis. Time to local and time to distant recurrence were computed from the date of primary tumor resection to the date of local or distant recurrence. Local recurrences were ignored for the analysis of distant recurrences and vice versa. For both abdominal and distant recurrences analyses, death was considered as a censoring event. Univariate and multivariate prognostic analyses were performed for OS, abdominal and distant recurrences using the log-rank test and Cox proportional hazards models. The variables found statistically significant variables in any of the univariate analysis were retained in the multivariate analyses. Multivariate analyses were stratified on sex, age (< >50 years), and tumor size (< >20cm). Variables were selected with a backward selection algorithm; relative risks are given with their 95% confidence intervals. All tests were two-sided and the 5% significance level was used.

Table 2: Postoperative morbidity and mortality.

Total	n	%
Postoperative mortality	4	6
Postoperative morbidity	24	39
Emergent reoperation	11	18
Percutaneous drainage	4	6
Percutaneous vena cava filter	1	2
Peritoneal hemorrhage	4	6
Septic complications	11	18
Anastomotic fistula	4	6
Deep abscess	2	4
Peritonitis without fistula	2	4
Necrotizing pancreatitis	1	2
Prosthetic mesh infection	1	2
Unknown	1	2
Respiratory complications	5	8
Pulmonary embolism	2	3
Pleural effusion	2	3
Acute pulmonary edema	1	2
Thrombosis of great vessels	2	3
Cardiac complications	2	3
Atrial fibrillation	1	2
Myocardial Infarction	1	2

Results

Between 1994 and 2015, among the 304 patients operated in our center for a primary RPS, 62 patients (20%) were older than 70.

Demographics and perioperative treatment

Patient characteristics of all 304 patients are given in Table 1. Considering only the subset of patients older than 70, the median age was 75 (range: 70-85). The median tumor size was 26 cm [range 11-46]. Forty-six patients (74%) had mass-related symptoms at the time of diagnosis (pain, increased abdominal perimeter, dysuria, constipation, gastro-esophageal reflux). Five patients (8%) had a RPS extended in the lower limb. The most frequently encountered histological subtype was liposarcoma (76%). Chemotherapy was given preoperatively to 6 patients (10%) and postoperatively to 1 (2%). Fifteen patients (24%) had radiotherapy, 7 (11%) preoperatively and 8 (13%) postoperatively. 54 patients (87%) had a first tumor resection and 8 patients (13%) had a second surgery after inadequate resection outside our tertiary care center. Compared to the younger population, less patients older than 70 had preoperative chemotherapy (p=0.009) or postoperative radiotherapy (p=0.024) (Table 1).

Type of surgery

At the time of surgery, 2 patients (3%) were deemed unresectable and underwent exploratory laparotomy (one patient because of the

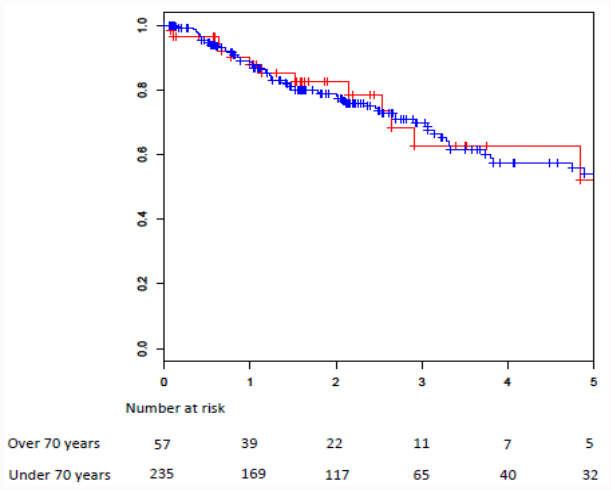

Figure 1: Locoregional relapse free survival according to age.

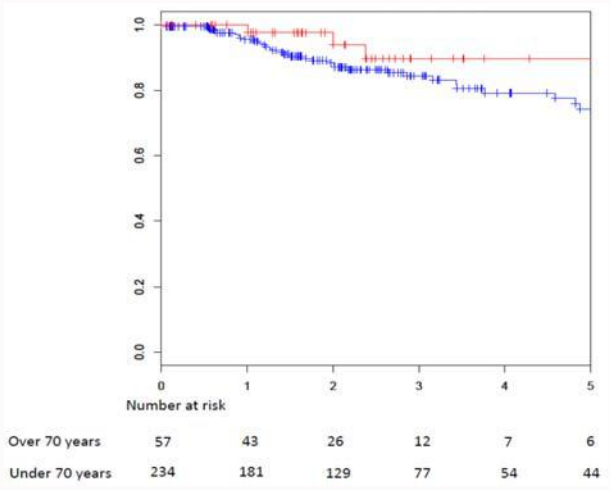

Figure 2: Overall survival according to age.

intraoperative findings of a vascular invasion of the iliac vessels and the other because of the intraoperative findings of an extensive synchronous peritoneal sarcomatosis). Sixty patients underwent resection and 58 (94%) had a macroscopically complete tumor removal. The reasons for incomplete resection were an intra-thoracic extension of the disease with a close contact to the aorta and a massive unexpected peroperative bleeding from a lumbar vein wound that required a shortened laparotomy. No tumor rupture was recorded in patient after complete resection. The surgery was performed without any organ resection in 6% of patients, with the resection of one organ in 8% and with the resection of multiple organs in 84%. Colon-rectum and kidney were the most frequently resected organs, in 84% of patients. Concerning resection with the potential for high postoperative morbidity, 4 patients (6%) had a spleno-pancreatectomy, 3 patients (5%) had great nerve resection, and 2 patients (3%) had great vessels resection (iliac vein in both cases). No patient required a definitive stoma, either digestive or urinary. The mean peroperative blood losses were 954ml (range: 15-5000) and 21 patients (34%) required a perioperative transfusion.

Postoperative morbidity and mortality

The in-hospital mortality was 6% (n=4). The causes of death were postoperative peritonitis after digestive anastomotic fistulas (n=2), massive air embolism after a peroperative inferior cava vein wound (n=1), and coma without identified etiology (n=1). Severe postoperative morbidity (including deceased patients) was 39% (n=24) and complications are listed in Table 2. An emergent surgery was required for 11 patients (18%). No patient had postoperative renal failure requiring hemodialysis. Compared to the younger population, higher rates of postoperative morbidity (p=0.020) and mortality (p=0.033) were recorded in patients older than 70.

Survival

After a median follow up of 20 months (range: 0-120), the 1-year, 3-year and 5-year OS rate were respectively 100% (IC95%: 100%-100%), 90% (IC95%: 79%-100%) and 90% (IC95%: 79%-100%). The median OS was not reached. At the last update, 8 patients had died. Cancer specific death rate was 86% (one patient died of unknown cause). No prognostic factors for disease specific survival were detected in the univariate and multivariate analysis.

Compared to younger patients, identical rates of 5-years OS (p=0.23) were recorded in patients older than 70. The results are illustrated in (Figure 1 and 2).

Recurrence

The 1-year, 3-year and 5-year DFS rate were respectively 88% (IC95%: 79%-98%), 63% (IC95%: 46%-85%) and 52% (IC 95%: 33%-84%). Median DFS was 94 months (range: 35-139). Thirteen patients had a loco-regional relapse among which 6 had an associated peritoneal sarcomatosis. The 5-years loco-regional recurrence-free survival (LR-RFS) rate was 52% (IC 95%: 33%-84%). The relapse was treated with chemotherapy in 7 patients, with radiotherapy in 3 patients and with best supporting care in 3 patients. Three patients developed distant metastasis. Distant metastasis were located in the lung (n=2) and in the liver (n=1). The rate of distant metastases occurrence at 5-years was 5% (IC95%: 0%-12%). In univariate analysis, factors significantly associated with loco-regional relapse in patients older than 70 were reoperation after inappropriate initial surgery (p=0.036), positive microscopic margins (p=0.023) and postoperative morbidity (p=0.045). In multivariate analysis, reoperation after inappropriate initial surgery (p=0.002) and postoperative morbidity (p=0.020) remained independent loco-regional relapse predictive factors. No predictive factor of distant metastasis or sarcomatosis was found. Compared to younger patients, identical rates of 5-years loco-regional relapse free survival (p=0.18) were recorded in patients older than 70. The results are illustrated in (Table 1), and (Figure 1 and 2).

Octogenarian patients

Eleven patients older than 80 were operated for a RPS in our series. Median age was 82 (range: 80-85). All patients had a first tumor resection. None of them received a preoperative treatment. The postoperative mortality was 18% (n=2) and the morbidity was 45% (n=5). Five patients (45%) required an emergent surgery (2 postoperative peritonitis for anastomotic fistulas, 2 bowel obstructions, 1 infected abdominal wall prosthetic mesh). One patient had postoperative radiotherapy, no patient had postoperative chemotherapy. One patient developed distant metastasis after 94 months (lung). No patient older than 80 died after hospital discharge after a median follow-up of 24months [1-117].

Discussion

We report a series of 62 selected elderly patients operated fora RPS, with a median tumor size of 26cm, among whom loco-regional

recurrence rates and OS rates were comparable to those of a younger population. The postoperative in-hospital morbidity and mortality in this elderly population fit for surgery was respectively 39% and 6%.

Population aging and geriatric oncology

The proportion of the elderly population is rapidly increasing in developed countries. Today in France, the life expectancy is 79 years for French men and 85 years for French women [10]. In 2040, people older than 80 could exceed 9% of the population [11]. With this aging of the population, we face new challenges. Nearly a third of all cancers occur in people older than 75 and we can expect an increased incidence of cancer in the next few years [12]. Even if there is no evidence based cut-off age to define an "elderly" situation, 70 to 75 years-old is often considered an arbitrary threshold in medical oncology. We encounter in this population specific elderly frailty, both medical and social, we need to cope with when treating these patients [12]. STS are not different from other cancer as their incidence is also increasing with age, even if the histological subtypes vary [13]. RPS represents a tremendous challenge because major abdominal surgery with multivisceral resection is the cornerstone of the curative treatment.

These consequences of this aggressive must be balanced when treating older patients with associated comorbidities and with a potentially increased postoperative morbidity and mortality [14].

Elderly patient's selection for surgery

Aging may be defined as a progressive decline in the functional reserve of multiple organ systems. This process is highly individualized, and poorly reflected in chronological age. The treatment of cancer should be based on the assessment of the physiological age, the patient's life expectancy and tolerance to the treatment. Physiological rather than chronological age should determine the management of cancer in each individual [15]. Of the various instruments proposed for the assessment of physiological age, a Comprehensive Geriatric Assessment (CGA) is the most reliable, as both cancer-independent mortality risk and functional reserve may be estimated based on the CGA (inability to perform the Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADLs), the presence of multiple morbidities, the cognitive status, the presence of geriatric syndromes, the nutritional status and the social support of the patient). In particular, the benefits of cancer treatment diminish with increased risk of non-cancer related mortality and of therapeutic complications. Comorbidity and functional status influence both [16-19]. With respect to the functional status, the ability to perform the basic Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADL) should be assessed in addition to traditional oncological measures of function, such as the Karnofsky scale and Eastern Cooperative Oncology Group (ECOG) performance status [20-21]. At present, there is no universal screening test that adequately identifies frailty in at risk older patients and most score were not available at the beginning of this study [22]. Selection process was prospectively based on ECOG scale and patient with a score less than 2 were deemed fit for surgery. In that selected population, we demonstrated that long survival could be achieved with an acceptable postoperative mortality. In the near future, the use of the new test could help to refine the patient selection for treatment.

Type of surgery and morbidity/mortality balance

Surgery enables the best results in non-metastatic RPS, with a 5 years OS of 67%, and a median survival of 116 months [4]. Because we found no difference between 5-years OS rates between older and younger patients in our series, we could expect the same results as in the literature when performing surgery on fit elderly patients. We found nevertheless higher rates of postoperative morbidity and mortality in patients older than 70 and that postoperative morbidity was an independent loco-regional relapse predictive factor. Decreased performance status and significant comorbidities could therefore determine the type of surgery, with a less extensive resection (i.e. colonic/digestive tract sparing) in frailer patient [23]. On the other hand, fit patient with a good life expectancy should undergo systematic in-bloc resection with adjacent viscera even when not overtly involved. In our series, complete surgery was possible with the resection of at least 2 organs in the most of the cases (84%). This aggressive surgical attitude could explain our good long term results, and even if mortality is increased, it remains acceptable compared to other cancer surgery frequently performed in elderly patients [24]. The studies who identified age as a significant independent prognostic factor could have been suffering from the bias of under-treatment in this elderly population [23]. One often neglected but important factor to also integrate when deciding the best treatment is the action of surgery on the symptom in these larges tumors.

Alternative treatments to surgery

Studies report the underuse of radiotherapy and chemotherapy in elderly patients [24-26]. In many prospective clinical trials, these patients are not included because of restrictive selection criteria. Recent studies nevertheless demonstrated that chemotherapy and radiotherapy could be well tolerated by elderly patients and was beneficial [26,27]. The same remark can be made for surgery, as cancer-directed surgery was demonstrated underused in elderly patients in a recent nation-wide american database, even in localized disease [26]. This study reported a significantly decreased odd of receiving surgery beginning at 60 years for lung cancer, at 70 years for liver cancer, and at 80 years for pancreatic cancer [26]. In our series, even if no difference concerning the survival was significant between the younger and the elderly population, we found less preoperative chemotherapy and less postoperative radiotherapy in the group older than 70. The natural life-expectancy at the actual age is a key factor to take in account when deciding a treatment. People often think of elderly patients as nearly in the grave when they are in fact survivors. In France, natural life expectancy at 75 is 14 years for a man and 18 years for a woman [28]. In our series, median survival after surgery was not reached after 20 months of median follow-up and only one out of 9 deceased patients died of non-cancerous cause. As an alternative to surgery, the reference chemotherapy in STS is since 30 years based on doxorubicin with/without ifosfamide, with a median OS in a metastatic setting of 13 months when using doxorubicin alone and 14months when using a combination of doxorubicin and ifosfamide [29]. Unfortunately, these toxic regimens can barely be used in elderly patients. Metronomic oral cyclophosphamide plus prednisolone is a seducing alternative in elderly patients with inoperable or metastatic STS [25]. With a good toxicity profile, it enabled a median OS of 14 months. There are few reports on irradiation results for inoperable RPS patients. In a phase II assessing carbon ion therapy in a limited dataset of unresected patients, outcomes were favorable (3 years actuarial overall survival and local control rates of 73% and 63%, respectively) and no severe acute and late reactions were reported [30]. In the absence of such technique Intensity Modulated Radiotherapy (IMRT) should be the preferred treatment modality as it could help reducing the high-dose irradiated volume within the intestinal cavity,

including the contralateral kidney [31]. Anyway, every decision of treatment in geriatric oncology should respect the four fundamental ethical principles (benevolence, non-maleficence, equity, autonomy) but the maintenance of an ethical reflection should not become a pretext for a systematic under-treatment [29].

Strengths and weaknesses

This study suffers several biases. Besides its retrospective design, we only studied patients deemed fit for surgery and could not evaluate unfit/inoperable patients. The performance status is missing as well as the ASA score. Nevertheless, we were able to identify a large population of elderly patients operated for a RPS in a high volume specialized center and were able to demonstrate the feasibility of major abdominal surgery and long term survival.

Conclusion

Complete resection with adequate surgical margins for RPS is feasible in selected elderly patients with an acceptable postoperative morbidity and mortality. It potentially enables longer survival than chemotherapy alone with a direct action on symptoms. Future studies should focus on selection process.

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