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Did outcomes improve in retroperitoneal sarcoma surgery?

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ABSTRACT

In the last decades, the deeper understanding of the biological basis of the disease, along with the advances of surgical techniques and oncologic multimodal treatments, have led to an overall increase of survival of cancer patients. However, significant amelioration of the prognosis of rare and under-investigated tumors such as soft tissue sarcoma is less evident. In this review, main changes in the surgical management of retroperitoneal sarcoma (RPS) are discussed in order to figure out whether actual improvement in RPS outcome has been occurred in the last years.

1. Introduction

The outcome of patients who have undergone surgery is generally driven by several factors including surgical technique, tumor biology, multimodal combined therapy, peri-operative management and, of note, patient characteristics and biology [Fig. 1].

In the past decades, the advances of surgical techniques and oncologic multimodal treatments, along with the deeper understanding of the biological basis of the disease have led to an overall increase of survival of patients affected by cancer.

However, some disparities may be observed among different kinds of cancers. The most common cancers are also the most studied ones, therefore these histotypes usually see a more pronounced improvement of diagnosis, therapy and prognosis. On the contrary, significant improvement of the prognosis of rare and under-investigated tumors is less evident.

Sarcomas are rare tumors representing less than 1% of all new cancer diagnoses. Retroperitoneal sarcoma (RPS) accounts for about 15% of all soft tissue sarcomas with an incidence of approximately 0.5–1 case per 100.000. Well or dedifferentiated liposarcoma (50–63%) and leiomyosarcoma (LMS) [1] are the most common subtypes followed by solitary fibrous tumor, undifferentiated pleomorphic sarcoma (UPS), synovial sarcoma and malignant peripheral nerve sheath tumor as well as other rarer sarcoma subtypes [2–5].

Complete surgical resection, often requiring challenging multi-organ resection, is the mainstay of treatment of RPS. Indeed, surgery represents the only chance for cure, being local recurrence, rather than distant relapse, the major determinant of long-term outcome. Conversely, the role of chemotherapy in the management of localized RPS is still unproven and the potential benefit of radiotherapy (RT) remains controversial and it is currently under evaluation (EORTC 62092-22092 STRASS trial).

2. The importance of radical surgery

Given the rarity and the heterogeneity of this malignancy, it is not easy to plan successful prospective randomized trials and to extrapolate strong evidence from retrospective studies. Similarly, it may be of some difficulty to analyze the change in management and prognosis of RPS over time.

Considering that there was no real breakthrough, neither in the biomolecular characterization, nor in the treatment of the different subtypes of sarcoma up to now, the outcome of RPS may be influenced by all the factors reported in Fig. 1; still, the quality of surgery remains probably the most relevant variable.

During the second half of the past century we observed an increase of the aggressiveness of surgical management of RPS, leading to a lower rate of non-resected tumors. The higher resection rate was generally related to higher overall survival (OS) of the patients. In their pivotal study published, Lewis and colleagues reported a resection rate of 83% and a 5-year OS of 70% in 500 patients operated for primary or recurrent RPS at the Memorial Sloan Kettering Cancer Center (MSKCC) between 1982 and 1997 [6]. These results were significantly better if compared with most of the previously published series [6–11]. The Authors also highlighted the need of an aggressive surgical approach to obtain negative margins and a complete surgical resection especially in

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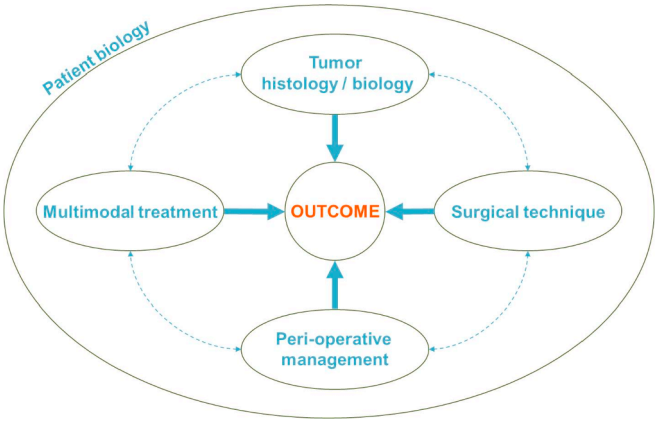

Fig. 1. Major determinants of outcome in cancer patients.

primary RPS [6].

A fair improvement of RPS survival is also evident comparing the results of two consecutive analyses of the US Surveillance, Epidemiology, and End Results (SEER) database [12,13]. In the former paper analyzing 1365 patients undergoing resection of primary RPS from 1988 to 2005, Nathan et al. showed a 5- and 10-year survival of 47%, and 27%, respectively [12]. The latter study, published by Giuliano and colleagues in 2016, reports a 5- and 10-year OS of 58.4% and 45.3% in 2920 patients operated from 2002 to 2012 [13]. Despite several limitations given by the retrospective nature of the studies and by the not negligible rate of missing data regarding histological grade, tumor size and completeness of resection, these SEER studies present generalizable information on outcomes after surgical resection of RPS in two different time periods.

3. Compartmental resection

Fig. 2 shows 5-year OS, 5-year local recurrence free survival (LRFS) and complete resection rate in the most representative surgical series of RPS. The correlation between complete resection rate and outcome is evident and portrays a slight but continuous improvement over time.

A significant step towards a more aggressive surgical approach is represented by the two landmark studies published by Bonvalot and Gronchi in 2009 [14,15]. In the former study, reporting on 374 primary RPS operated in France between 1985 and 2005, median OS was 6 years with 1-, 3- and 5-year OS of 86%, 66% and 57%, respectively. Gross complete resection (R0/R1) rate was 75% and 120 patients underwent the so-called “compartmental resection”, defined as the systematic resection of uninvolved organs performed to get a rim of normal tissue around the tumor (like in limb sarcoma surgery); conversely, in 195 cases a standard procedure was done (i.e. simple

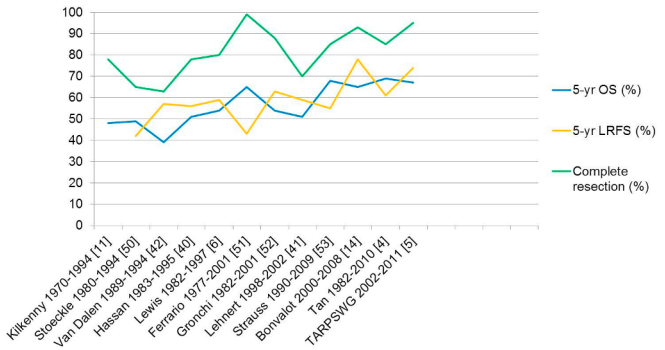

Fig. 2. Overall survival (OS), Local recurrence free survival (LRFS) and rate of complete resection in main surgical series on retroperitoneal sarcoma [4–6,11,14,40–42,50–53].

complete resection or resection of macroscopically involved adjacent organs). Grade, tumor rupture, gross residual disease and positive margins were found to be independent prognostic factors associated with OS. Also, a decreased abdominal recurrence rate was observed in patients with low grade tumor, no rupture, negative histological margins, operated at a high volume center and with a compartmental resection. This aggressive surgical approach was associated to a 3.29-fold lower rate of local relapse and a 3-year recurrence of 10% compared with 50% of patients who underwent standard surgical procedure [14].

In the same issue of *Journal of Clinical Oncology*, Gronchi and colleagues from Milan reported their single-institution experience on 288 RPS demonstrating a greater local control of disease by the adoption - from 2002 onward - of a more liberal visceral en-bloc resection approach (i.e. compartmental resection). Patients who underwent extended surgery experienced a 5-year local recurrence rate of 28% compared with 48% for patients who were treated with the standard approach. Other important independent variables for local recurrence free survival were tumor grade, histologic subtype and radiation therapy [15].

In 2010, the French and the Italian groups published a combined series including 249 primary RPS treated by a frontline aggressive surgical approach from 2000 to 2008. The Authors reported a complete macroscopic resection rate of 93% with a median number of organs removed en-bloc with the tumor of 2 (range 0–8). The 5-year OS was 65.4% and local recurrence (LR) and distant metastasis (DM) incidences were 22.3% and 24.2%, respectively [16]. Post-operative major surgical morbidity and mortality rate were 18% and 3%, respectively. A surgical re-operation was needed in 30 patients (12%). Importantly, the risk of post-operative morbidity increased only when more than three organs were resected and surgical complications were not related to oncological outcome. On the basis of these results, the Authors concluded that a frontline aggressive surgical approach to primary RPS was safe if performed at high volume centers [16].

Few years later, Gronchi et al. presented an updated analysis of patients operated at their Institution for primary or recurrent RPS in order to obtain additional data on long-term survival [17]. The 331 patients included in the analysis were divided into two groups according to the date of surgery (before and after 2002) as previously done in the paper of 2009.

Whereas no significant difference in terms of completeness (R0-1 vs. R2) of resection was found between the two groups, a marked higher number of resected organs was observed in the recent group. Five-year OS, 5-year incidence of LR and DM were 66%, 28% and 25% in the second group compared with 48%, 49% and 12% in the first group. The only other independent prognostic factor for OS was histological subtype. The prognostic benefit conferred by the extended surgical approach was clearer in the low and intermediate grade tumor and it was confirmed also in the recurrent RPS subgroup [17]. In brief, the adoption of compartmental resection was demonstrated to give an improvement in terms of local disease control and OS, whereas no benefit in lowering distant metastases incidence was found.

4. Criticism

Since the publication of the first studies in 2009, several criticisms about the real value of a frontline aggressive surgical approach to RPS were raised mainly from some leading Institutions in the United States [18]. The main concerns regarded both methodological and technical surgical aspects. The retrospective nature of the data incorporated unavoidable and potentially confounding bias, such as the lack of standardization in tumor imaging, operative technique or processing of the pathological specimen. Also, the selective resection of uninvolved tissues with the sacrifice of organs whose resection was considered “low-morbidity” (i.e. colon, kidney, psoas), while preserving high risk structures (pancreas, liver, duodenum, large blood vessels), might eventually lead to obtain wider negative margins only in some selected

areas and not all around the sarcoma. Other relevant issues raised, regarded the not negligible rate of post-operative complications or re-operation rate associated with an aggressive surgical approach, and the potential role of adjuvant therapy (radio and/or chemotherapy) offered to the patients included in the different studies.

In an editorial of 2015, Crago from MSKCC suggested that the observed improvement in patients treated by compartmental resection in recent series might be associated with an improved ability of selecting patients who were most likely going to benefit from surgical resection [19].

Another argument against a frontline aggressive surgical approach lies on the good survival results reported by Institutions where a compartmental resection was not systematically employed.

In their retrospective study including 132 patients who underwent surgery for primary RPS with a selective use of multivisceral resection (i.e. only when structures were grossly infiltrated or inseparable from the tumor), Bremjit and colleagues showed 94.4% of complete macroscopic resection (i.e. R0/R1) with a 2-year and 5-year OS of 85% and 71%, after a median follow-up of 31.8 months [20].

More recently, Tan and colleagues published a large series including 675 patients surgically treated for primary RPS at MSKCC, from 1982 to 2010 [4]. In 42% of cases no organs were removed with the tumor and a macroscopically complete resection was achieved in 574 patients (85%); additional non-surgical therapies were administered in 27% of patients. After a quite long follow-up of 7.5 years for survivors, they reported a 5 and 10-year disease specific survival (DSS) of 69 and 55%, respectively; cumulative 5 and 10-year LR were 39 and 45%, whereas the incidence of DM was 24 and 29% after 5 and 15 years. R2 resection, resection of 3 or more contiguous organs, and histological type were independent prognostic factors related to DSS. The Authors highlighted that observed DSS rate was similar to the 5-year OS of the recent French and Italian series where both compartmental resection and higher rates (60–70%) of radio and chemotherapy were used [4].

Moreover, in a previous report from the same Institution, Singer and colleagues found that the need for contiguous organ resection (kidney excluded), along with dedifferentiated histological subtype, was related to a higher incidence of local and distant relapse of the disease [21].

The recently published retrospective study by the MD Anderson on 83 primary well differentiated RP liposarcoma, reported a 92% of complete resection with 46% of patients who underwent concomitant organ resection; 5-year OS and DFS were 86% and 51%, respectively, after a median follow-up of 7.3 years. The Authors also showed that concomitant organ resection was not related with survival but it was associated with increased post-operative complications, recommending resection of contiguous organs only in case of suspected invasion [22]. The same group confirmed this recommendation also in recurrent well differentiated RP liposarcoma in a simultaneous paper [23].

Tseng and colleagues reported a not negligible risk of multifocal (two or more lesions in the same compartment) and/or multicentric (two or more synchronous tumors in non-contiguous compartments) disease in patients affected by well-differentiated and dedifferentiated liposarcoma, recommending that compartmental resection should be considered with caution in these sarcoma subtypes [24]. The Authors also suggest this finding may support the theory hypothesizing that recurrence in some liposarcoma patients may be due to a field defect in retroperitoneal and intraabdominal fat [25]. This could potentially argue against compartmental resection considering the difficulty to obtain a complete clearance of all abdominal (including mesenteric) fat and the related high morbidity.

However, it is worthwhile to consider that the observed heterogeneous results across experienced sarcoma centers may reflect the influence of selection bias and confounding factors, rather than the actual effect of the surgical approach.

In brief, complete gross (i.e. macroscopically complete) resection is the best chance for cure of RPS, but there is controversy about how aggressive surgery should be.

5. The Trans-Atlantic RPS working group

This ongoing debate has generated renewed interest in the scientific Community, leading to an improved effort in organizing multicentric international collaborations in order to standardize and improve the quality of management of RPS. For this purpose, an RPS Trans-Atlantic working group (TARPSWG) was established in 2013 [3] by inviting to participate high volume sarcoma centers mainly from Europe and North America. This working group produced consensus papers on the treatment of primary and recurrent RPS in the last years. It is worthwhile to note that the major sarcoma centers in USA (MD Anderson Cancer Center and MSKCC) chose not to participate in writing these guidelines, due to some concerns regarding the difficulty to generalize care of patients with rare histotypes, heterogeneous clinical scenarios and criteria to define a high-volume sarcoma center [26].

Beyond criticisms, in 2016, this international cooperation led to publish the largest retrospective series of primary RPS including 1007 patients treated at 6 European and 2 North American Institutions between January 2002 and December 2011 [5]. A R0/R1 resection was achieved in 95.3% of patients and 1 or more than 1 organ were resected en-bloc with the tumor in 87% of cases. After a median follow-up of 58 months, the 5, 8 and 10-year OS was 67, 56 and 46%; the incidence of LR was 25.9, 31.3 and 35% after 5, 8 and 10 years; 5-year DM rate was 21 and 21.6% after 8 and 10 years. Tumor size, histological subtype, grade, multifocality and completeness of resection were independent prognostic factors for outcome. Importantly, the pattern of recurrence significantly varied among the different histological subtypes, with well differentiated liposarcoma (WD-LPS) and leiomyosarcoma (LMS) representing two extremities of the spectrum. Indeed, the former was characterized by a significant rate of LR with virtually null risk of metastases, whereas the occurrence of DM was the main pattern of failure in LMS. Moreover, the incidence of LR after 8 years in WD-LPS was 5% in the center where extended surgery and RT were employed, about 35% in the one where RT was not employed, but surgery was extended, and 42% where RT was not employed at all and surgery was more limited. However, no statistically significant differences in OS were observed among the Institutions. Interestingly, the different therapeutic approaches did not influence LR, DM and OS in LMS subgroup [5].

6. The role of histology

Leaving aside the controversy about compartmental resection, one of the main results achieved by the TARPSWG paper was to demonstrate on a large study population basis the leading role of histology (i.e. biology of disease) in determining the natural history of the disease and, thus, the outcome of the patient. Therefore, histology should be taken into consideration when planning the treatment, in order to counterweight the expected outcome improvement with the possible adverse events.

The importance of histology subtype in RPS was already suggested by a paper from MD Anderson evaluating the prognostic accuracy of a three-tiered classification system on 343 patients with primary or recurrent RPS. Patients were divided by histology in atypical lipomatous tumor (ALT), non-ALT liposarcoma (LPS) and other sarcomas identifying distinct prognostic groups with patients affected by LPS or other sarcomas showing a worse prognosis [27].

Histology was found to be the most powerful prognostic factor associated with OS, LR and DM also in the large series published by the MSKCC group in 2016 [4].

Moreover, the adoption of a histology-based classification of RPS makes it easier to compare patient characteristics and outcomes between different Institutions.

For example, analyzing the aforementioned two large series published by TARPS and MSKCC groups it is easy to note that the outcome of patients affected by WD-LPS and LMS are quite similar in terms of

survival and DM [4,5]. Gronchi and colleagues reported a 5-year OS of about 90% and 60% for WD-LPS and LMS, respectively, whereas the 5-year probability of death due to disease was 10% and 40% for WD-LPS and LMS in the paper by MSKCC. The incidence of DM after 5 years in WD-LPS subgroup was virtually null in TARPSWG paper and less than 5% in MSKCC study; the risk raised up to 50% for patients operated for LMS in both groups. On the contrary, some differences could be observed in terms of local control of disease by Tan and colleagues, that reported a 19% and 38% of LR after 5 years from surgery for LMS and WD-LPS, respectively, compared with 9% and 22% published in Gronchi's paper [4,5].

Basically, the histological subtype represents the unique biological signature of each tumor: it determines the likelihood of organ invasion, the risk and patterns of recurrence and, finally, the overall survival of patients affected by RPS.

Although a controversy about the extent of surgery for RPS exists in the scientific community, all the authors converge on the foremost role of histology in driving a tailored patient therapeutic management. Therefore, the histology-based approach may solve the aforementioned controversy leading to a histology-guided surgery in which a compartmental resection is performed for aggressive tumors with high propensity to local recurrence, whereas a more conservative approach is reserved for less aggressive subtypes or with prevalent distant failure pattern.

In their recent interesting paper, Fairweather and colleagues from Harvard reviewed their experience on 118 primary RPS and proposed, for the first time, a classification system for perioperative clinical rationale for organ resection [28]. Importantly, they observed that both rationale for organ resection and histologic organ infiltration significantly varied according to different RPS subtype (i.e. well-dedifferentiated liposarcoma, dedifferentiated liposarcoma and leiomyosarcoma) providing a further basis for histology guided surgery. Considering that sparing organs with histologic infiltration may increase local recurrence rate - although not surely improving OS - the Authors recommend that a proper surgical strategy should require, at least, the removal of organs with high risk of infiltration [28]. Further efforts in merging experiences from several Institutions are mandatory in order to obtain adequate data on histology guided surgery, to develop common surgical strategies and finally to improve the outcome of patients with RPS.

Histology should also drive the treatment strategies helping in the choice of the optimal chemotherapeutic regimen and in the administration of radiotherapy.

An exhaustive dissertation of these aspects goes beyond the aim of this review, but it is worthwhile to highlight that the role of systemic therapy is controversial and currently unproven for most sarcoma subtypes [29].

Given the rarity of the disease and the little number of RCTs, data on chemotherapy regimens are mainly extrapolated from works on extremity sarcomas. RPS are, in general, insensitive to chemotherapy with some exceptions. Here we briefly analyze the CT response of major sarcoma subtypes by histology and grade.

For the most part, liposarcoma is only slightly sensitive to chemotherapy. However, advanced myxoid and dedifferentiated liposarcoma shows a significantly higher response rate compared to all other liposarcoma subtypes. The most used first line chemotherapy regimens include doxorubicin (successfully used in myxoid LPS) with or without ifosfamide, or gemcitabine with docetaxel [30,31]. In the second line advanced or metastatic setting, trabectedin and eribulin may be used. Doxorubicin combined with Olaratumab, a relatively new monoclonal antibody against the platelet derived growth factor receptor alpha, is now the standard of care for all sarcoma subtypes that may be sensitive to doxorubicin, including liposarcomas. Other attractive agents under evaluation are MDM2 or CDK4 inhibitors (palbociclib) and tyrosine kinase inhibitors (sunitinib) [29].

Several works suggest that any chemotherapeutic regimen used in the preoperative or postoperative treatment of leiomyosarcoma is ineffective and can even reduce the patient outcome (both OS and progression free survival) [32]. Although these evidences are extrapolated from retrospective studies, these are specific for RPS and are in line with data produced by available RCTs assessing the role of chemotherapy as therapeutic option in soft tissue sarcomas of any anatomical location. Uterine leiomyosarcoma seems to be more chemosensitive than any other leiomyosarcoma [29].

A higher response to chemotherapy is shown by less frequently occurring sarcoma histotypes, such as synovial sarcoma and Ewing's sarcoma. Synovial sarcoma is particularly sensitive to alkylating agents (ifosfamide), especially in the neoadjuvant setting. Synovial sarcoma is thus considered, by far, the most chemosensitive sarcoma [33]. Similarly, Ewing's sarcoma is generally well treated with neoadjuvant combination of drugs such as vincristine, doxorubicin, ifosfamide and etoposide followed by surgery or RT with subsequent consolidation therapy [34].

Rarer RPS such as malignant peripheral nerve sheath tumor (MPNST), undifferentiated pleomorphic sarcoma (UPS or malignant fibrous histiocytoma) and solitary fibrous tumor (STF) are largely chemoresistant. Systemic therapy has been tested in the neoadjuvant, adjuvant, palliative treatment of MPNST without impressive results, thus surgery remains the standard of care [29]. Despite the chemoresistance shown by UPS and its poor prognosis, doxorubicin-based regimens have shown some improvement in OS in both pre- and postoperative setting and in first-line treatment of locally unresectable or metastatic lesions. Ifosfamide, trabectedin, dacarbazine, pazopanib have also shown some efficacy in advanced UPS.

Similarly, no first-class evidences are currently available to support the routine use of peri-operative radiotherapy in RPS, but the awaited results of the STRASS trial (NCT01344018) may shed some light on this issue [35].

At present, the use of perioperative RT in RPS should be discussed in a multidisciplinary board to provide the patient with an individualized treatment that is an optimal combination of these two therapeutic strategies. Feasibility of RT and surgery should be considered together with surgical technical aspects, such as those deriving from working on an irradiated field. Pretreatment assessment of renal function should be standard of care, as well as surgical and RT planning for bowel and vascular resections. Kidney-sparing surgery or RT should be considered if a low renal function is detected; healthy, not previously irradiated tissue should be used for reconstructions (anastomoses) after bowel and vascular resections, in order to avoid lacerations or development of fistulas [35].

International expert consensus guidelines have been published for preoperative RT in RPS, and guidelines for the clinical target volume (CTV) and internal target volume (ITV) delineation are available [36]. An interesting concept is that of dose escalation, according to which the cancer portion at major risk for positive margins (usually, the part facing the posterior abdominal wall) should be treated with and increased dose of RT, while the whole tumor bulk is treated with a moderate dose (45–50 Gy) [37].

The pattern of use of RT for RPS is highly variable, with older studies using RT in an adjuvant setting and newer literature proposing RT as a preoperative therapy. Intraoperative RT, brachytherapy and intensity modulated protons have been used for the treatment of RPS, but with inconclusive results; thus, their employment is best advised on protocols [35].

Further international multi-institutional collaboration will be mandatory in order to run successful translational and clinical studies focusing on specific histotypes and individual subgroups.

7. Morbidity of RPS resection

The trend toward a more radical approach in surgery for RPS generated a vivid debate on operative morbidity and the possibility that

this may overcome the oncological benefit.

Smith and colleagues in 2015, analyzing 10-year experience at a center with high caseloads for RPS surgery, reported 292 (80.7%) resections including a contiguous organ, with a median of 2 organs resected per patient; in their series, 30-day mortality rate was 1.4%, severe adverse events occurred in 9% of patients and 7.5% required a reoperation [38].

In 2017, the TARPS working group investigated safety of radical resection for primary RPS in a multicenter series involving 1007 patients [39]. Severe postoperative complications (classified as Clavien-Dindo ≥ 3) occurred in 16.4% of patients and 10.5% of cases required reoperation; 30-day mortality rate was 1.8%. The most frequent complications were bleeding/hematoma (2.9%) and anastomotic leak/fistula (2.6%). In order to more objectively stratify and compare morbidity in multivisceral resection, resected organ score – a simple and quick score where different organs have their specific weight (i.e. pancreaticoduodenectomy has a higher score than nephrectomy, while organs whose removal does not add any morbidity accounts for 0) – was introduced and applied in this series.

Univariate analysis found out severe adverse events to increase significantly together with age and resected organ score; multivariate analysis confirmed these two parameters (and not the number of resected organs) to be predictive of postoperative morbidity. Moreover, at multivariate analysis the need of transfusions resulted an independent prognostic factor; however, it is a multifactorial variable and its value should be cautiously considered. Administration of preoperative chemo- or radiotherapy was not related with an increase in post-operative morbidity, indicating that also patients who undergo multimodal therapy can be safely treated without any relevant impact on surgery.

In addition, pattern of multivisceral resection resulted to be relevant, being surgery including pancreatico-duodenectomy, major vessel resection and splenectomy/pancreatectomy related to a higher risk of postoperative complications. Of note, no relationships between surgical morbidity, oncological outcome and OS were found [39].

Few data about morbidity of RPS surgery in pre-radical resection era are available. In a series including 278 patients who underwent surgery for primary RPS between 1982 and 1997 at MSKCC, 77% of patients had at least one organ resected with a 30-day mortality rate of 4% [6]. Out of the 97 patients surgically treated for primary RPS at the Mayo Clinic between 1983 and 1995, 48 (63%) had adjacent organs resected en bloc with the tumor and only 22 (27%) had more than one organ resected. Major complications occurred in 7 patients (8%) and 6 (6%) required surgical management; in-hospital mortality rate was 2% [40]. A German single institutional study on 110 patients with both primary and recurrent RPS, and who underwent surgery between 1988 and 2002, reported complete resection in 70.4% of primary RPS; 64 (58.2%) patients underwent multivisceral resection (39 for primary disease and 25 for recurrence); 30-day mortality occurred in 6.4% of patients and overall complication rate was 26%, with no difference between patients treated for primary or recurrent disease [41].

Van Dalen and colleagues reported that 63% of patients underwent radical resection (R0/R1) in a sample of 143 patients with primary RPS between 1989 and 1994; 30-day mortality rate was 4% [42].

Although surgical details are not always available and it is sometimes difficult to compare results from different studies, it is to note that mortality rate in patients who underwent radical resection is not higher than that observed in patients treated with a less aggressive surgery.

In 2008 Lahat and colleagues compared alternative surgical approaches based on histological subtype. Out of 135 patients submitted to surgery for primary or recurrent RPS from 1996 to 2007, 77 had dedifferentiated tumors, therefore received a more radical surgery than the remaining 58 patients who were affected by well-differentiated liposarcoma. Most of the patients (53.4%) with well differentiated tumors underwent marginal resection without adjacent organs resection, while 71.4% of patients with dedifferentiated liposarcoma had a multivisceral resection. Overall morbidity was 15.5% in limited surgery and 35.1% in radical resection, while mortality rate was 0% and 3.9% respectively [43].

The outcomes of most of the above-mentioned studies are representative of results in referral centers. In 2011, Tseng and colleagues published data on resection of retroperitoneal tumors analyzed from the American College of Surgeons National Surgical Quality Improvement Program (ACSNSQIP) database in 255 hospitals including both community and academic centers [44]. Considering 156 patients surgically treated for retroperitoneal neoplasms, 63% of them had marginal resection, 37% underwent resection of an adjacent organ and only 6.4% received a multivisceral resection. Thirty-day mortality was 1.3%, severe complications occurred in 22.5% of cases and 4.5% required reoperation. However, it is to note that no differences in overall morbidity, severe morbidity and mortality were observed between patients treated with limited excision and those subjected to contiguous organ resection. However, a limit of this study is the lack of data on important confounding factors such as tumor histology, resection margins, surgeon expertise and hospital case-load [44].

Despite limited and heterogeneous data in Literature, results from available retrospective studies seem to show that morbidity rate in radical resection is at least not worse than in limited surgery. In order to design the best treatment strategy in each patient, sarcoma surgeons should be able to provide expected morbidity of a planned procedure.

8. Referral centers

The heterogeneity and rarity of RPS, the need of tailoring the treatment on the basis of histological subtype and on individual patient and tumor features, makes it mandatory to treat this disease in referral centers, since the management requires highly specific expertise. It is worthwhile to highlight that the best chance of cure relies on the adequacy of surgery at the time of presentation. In particular, the expected benefit in terms of oncological outcome needs to be balanced with possible post-operative morbidity.

The diffusion of new health policies, which aimed at the improvement of standards of care and best practice, have significantly lowered surgical morbidity and mortality in the last decades [45,46]. Also, the inverse relationship between hospital volume and mortality was documented in several types of major surgery [46] and this could apply also for RPS surgery. In 2007, Gutierrez et al. published their study analyzing the outcome of 4025 patients with soft tissue sarcoma registered in the Florida Cancer Data System on the basis of the operative volume of medical Institution [47]. Overall, the majority of patients were operated at low-volume centers but most surgeries for high grade sarcoma or tumors over 10 cm were carried out at high-volume hospitals. Thirty-day and 90-day mortality rate were 0.7% and 1.6% for high-volume and 1.5% and 3.6% for low-volume centers, respectively. Importantly, univariate analysis showed significantly improved survival in high volume centers especially in patients with high grade, large or truncal and retroperitoneal sarcoma. At multivariate analysis, treatment at high volume center was an independent prognostic factor [47].

A retrospective analysis on 586 RPS from the French Sarcoma Group confirmed the crucial role of an appropriate pretreatment assessment and identified surgery in a specialized center as the most important prognostic factor, along with avoiding piecemeal resection of the tumor [48].

More recently, 3141 non-metastatic RPS from the US National Cancer Database were analyzed by Maurice and colleagues, in order to assess the association between hospital volume and outcome [49]. Seventy percent of patients who underwent surgery reported a R0/R1 resection rate of 93.0% and 67.6% of R0. Surgery, R0/R1 resection, and R0 resection were found to be associated to prolonged overall survival. Of note, patients treated at high-volume hospitals had 1.9-fold higher odds of undergoing surgical management, 2.5-fold higher odds of receiving a R0/R1 resection, and 1.8-fold higher odds of an R0 resection

[49]. All these data together support the need for further centralization of RPS management to achieve optimal outcomes and they should stimulate National authorities to increase the efforts towards accreditation for centers of sarcoma surgery.

9. Conclusion

In conclusion, the outcome of RPS improved in the past decade mainly due to a more aggressive surgical approach, a deeper understanding of tumor biology and the centralization of cure. The role of the neoadjuvant RT is currently under evaluation and it may add some benefit to local disease control. The development of new and effective drugs is mandatory to address the "systemic risk" in some sarcoma subtypes. In this field, the characterization of soft-tissue sarcomas is still evolving from "classical" pathology toward new histological features, immunohistochemical biomarkers and improved knowledge of the underlying genetic variations. Moreover, emerging gene-array and proteomic techniques are being increasingly applied to identify potential treatment targets, which may help to individualize therapy.

Therefore in many aspects, collaboration through clinicians and researchers from different specialized referral Institutions from all over the world is paramount to improve the outcome of patients affected by such a complex disease as RPS.

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