

Frontline Extended Surgery

Subjects: **Surgery**

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Surgery is the only curative treatment for localized disease in retroperitoneal sarcoma (RPS). Frontline extended surgery, or compartmental surgery, is a surgical strategy consisting of resecting the tumor together with adjacent organs, with the aim of minimizing marginality.

retroperitoneal sarcoma

liposarcoma

leiomyosarcoma

solitary fibrous tumor

1. Introduction

Retroperitoneal sarcomas (RPS) represent <1% of all adult malignancies, and account for about 15% of all soft-tissue sarcoma with s (STS). Under the definition of RPS a large number of different histologies can be found, whose common characteristic is its critical anatomical location [1]. Arising from the retroperitoneal space entails a growth in a “compartment” without anatomical limits and surrounded by vital structures. Hence, there are no “low-risk histologies” as with STS of the trunk and extremities, and even low-grade RPS have high rates of local failure, which undermine long-term survival. The anatomical complexity of the retroperitoneum and the biological heterogeneity of the different RPS entail difficult challenges for their management. Surgery is the key element in RPS treatment, being the only curative therapy in localized disease. Retrospective historical series evidenced that R0 resection was the most important prognostic factor related to treatment, and the only factor where the surgeon could make a difference [1][2]. In recent years, there has been a progressive increase in R0 resection rates, up to 70–95%, which shows a trend towards more aggressive surgical policies and a better selection of patients [3][4]. With the aim of improving long-term oncological results of RPS, a new surgical strategy based on the principles of compartmental surgery for STS of extremities has been proposed. This surgical approach, known as frontline extended resection, consists of an en bloc resection of the tumor together with adjacent organs, with the aim of minimizing marginality (R1-2 resections) in the retroperitoneum. This surgical approach has been standardized and is currently the recommended approach by the main groups of experts [5][6][7][8]. However, in RPS there are multiple prognostic factors such as histologic subtype, tumoral grade, age, or multifocality which can predict the pattern of recurrence and may guide the aggressiveness of the surgery or the need for complementary systemic treatment [9].

2. Frontline Extended Surgery

The compartmental surgery for STS of extremities is based on the resection of the anatomical compartment where the tumor lies and has demonstrated that resection margin status is key on disease-free survival and overall survival of sarcoma patients [10]. In STS, four types of resections are classically defined [11]: intralesional (R2), marginal (through the tumor pseudocapsule) (R1), wide (i.e., with a margin of healthy tissue), and radical (i.e., en

bloc resection of the anatomical compartment). Since there are no defined anatomical compartments in the retroperitoneum, surgery for RPS will always be a marginal resection. Acknowledging the above, the need for an optimal resection strategy in RPS was postulated: the frontline extended approach, also known as compartmental surgery. This extended surgery includes the tumor and adjacent organs located at 1–2 cm from the tumor, including the colon anteriorly, kidney, and psoas muscle posteriorly, even if there is no macroscopic organ invasion. These organs can be safely and easily resected with limited impact or comorbidity, in contrast with other critical structures such as the duodenum, pancreatic head, or vertebrae, where a marginal resection is favored.

Through this approach, the ipsilateral retroperitoneal fat is resected by means of intrabdominal dissection beyond the anatomical barriers, ensuring the elimination of potential satellite metastases, optimizing surgical margins, and increasing the possibilities of obtaining an R0 resection. This also reduces the persistence of microscopic disease and tumor dissemination [4][11]. This extended approach can reduce local relapse (LR) rates, and, consequently, increase overall survival (OS) given that RPS local failure is the main cause of death related to the tumor, considering many patients will die without distant metastases. However, the appropriate extent of resection in RPS remains a topic of debate, while the benefit of converting R1 to R0 resection has not been proven, prevention of R2 resections is crucial. The impact of microscopic surgical margins in extremity and trunk sarcoma has been well established, which has not been the case with RPS. Nevertheless, surgery should aim to remove the tumor completely to minimize marginality. There are several reasons for this uncertainty on margin assessment in RPS. The main one is the lack of a standardized protocol for pathologic sampling, as RPS specimens are big masses, arising from a virtual space (retroperitoneum), which is difficult to replicate on the pathologist's table.

A few years ago, A. Gronchi (Istituto dei Tumori, Milan) [5] and S. Bonvalot (Institut Curie, Paris) [6] first described the concept of compartmental surgery in the retroperitoneum, with the aim of improving local control of RPS. In 2009, these authors presented the first retrospective series, from a 20-year period, on oncological outcomes after the implementation of this new surgical policy on RPS treatment. The multicenter study by S. Bonvalot showed that simple resection was associated with a threefold higher rate of local recurrence than compartmental resection, while A. Gronchi and his group, analyzing the change in surgical policy in their institution (simple resection—before 2002—vs. compartmental resection 2002–2009), showed a decrease in local recurrence (LR) at 5 years of 48% vs. 28% in the extended surgery group. These studies showed that margin status was a key prognostic factor on LR as a consequence of a more liberal organ resection strategy. No significant difference in terms of completeness (R0-1 vs. R2) of resection was found between the two groups, nor could they prove an advantage in OS from compartmental surgery. However, subsequent follow-up of these series has shown that compartmental surgery can improve OS, especially in low- and intermediate-grade liposarcomas, with a morbidity and mortality comparable to that of other oncological abdominal surgeries. The study and effort of these two European groups consolidated the current scientific basis of frontline extended surgery for RPS [11][12].

The retroperitoneum cannot be considered a real compartment due to the absence of anatomical boundaries and the presence of vital structures at its limits. However, there are natural barriers to tumor dissemination, such as the fascia of the psoas muscle, the vascular adventitia, or the peritoneum, which help to define the surgical space. These anatomical barriers will be altered with large tumor growths or because of multiple reinterventions due to

local recurrence. In RPS surgery, the encased organs such as the colon and mesocolon, the kidney, or the pancreas become the oncological margins of the RPS. The rationale for this extended surgery is the liberal resection of the ipsilateral colon, kidney, and adrenal gland—anterior margin—and psoas muscle—posterior margin—en bloc with the tumor, thus clearing all ipsilateral retroperitoneal fat. The vascular dissection is performed through the adventitial plane, and vascular resection of main vessels would only be performed in case of tumor invasion. Spleen, pancreatic tail, or diaphragm would only be removed with very large left upper quadrant tumors. More aggressive resections such as duodenojejunal junction, pancreatic head, rectum, bladder, or the vertebral bodies will only be performed in highly selected cases when a clear tumor infiltration exists.

Given the sacrifice of healthy organs without tumor invasion together with the tumoral mass, this multivisceral “liberal” resection policy has received considerable criticism [13][14][15], generating a heated debate within the scientific community about the oncological value of compartmental surgery in terms of OS compared to the morbidity and mortality associated with such aggressive surgical strategy. In order to evaluate the physiological reasons of this approach, some studies have analyzed the histopathologic organ invasion (HOI) of the resected organs together with the RPS. These showed that up to 25% of the resected organs without intraoperatively evidence of tumor invasion had HOI identified pathologically [14]. That fact justifies a more extended approach to secure margins in RPS. In 2017, a study from Dana Farber/Brigham and Women’s Cancer Center demonstrated that HOI was an independent predictor of adverse prognosis with a worse 5-year OS (34% vs. 62%, $p = 0.04$). In this study, 26% of resected organs demonstrated HOI [16]. However, HOI should be considered as a marker of biologic aggressiveness rather than the rationale for organ resection, which should be guided by RPS histology. The pathological evaluation of HOI is difficult and has not been standardized yet. In sarcomas, HOI should not be just defined as the infiltration of visceral parenchyma, but also as the tumor adherence to the organ. For instance, in RP-LPS, detaching the tumor from an adherent organ will guarantee an R1 resection. Regarding surgical morbidity, the major retrospective series reflects that these interventions are safe when carried out in reference centers counting with multidisciplinary teams (MDTs) with a high volume of patients, whereby pancreatic and vascular resections are associated with higher surgical risk [17]. It has been recently reported that there is not an association between surgical morbidity and long-term oncologic outcomes [18].

Recently, Callegaro et al. have published a multi-institutional study of 1942 RPS resected patients, investigating the outcomes related to the changes in treatment strategy during 2002–2017 at 10 sarcoma referral centers. Their study describes how the rate of R2 resection decreased and the median number of resected organs increased over time. It concludes that the long-term survival of RPS patients who underwent resection had increased during the last 15 years, with the best survival outcomes at the last period of the study (2012–2017). This is a confirmatory study of how a better selection of patients and quality of surgery (i.e., a decrease in R2 rate and intraoperative tumor rupture, and the adoption of a more aggressive approach) increase disease-specific survival in RPS [19].

Due to the rarity and heterogeneity of RPS, the prospective randomized trials are lacked, and it is hard to extrapolate strong evidence from retrospective studies. However, an increase in survival rates in recent years in resected RPS denotes that a liberal en bloc resection of the tumor with adherent organs, even if not infiltrated, tailored to each histologic subtype, tumor localization, and patient performance status and comorbidities should be

the gold standard for RPS surgery [20][21]. Compartmental surgery has been advocated by the masters of sarcoma surgery [9][22] and recommended by supporting guidelines [23].

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