

Patterns of Recurrence in Retroperitoneal Liposarcomas: Reflecting Surgical Approach or Tumor Biology?

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Complete surgical resection remains the mainstay of curative treatment for retroperitoneal sarcomas (RPS) and provides the only hope for long-term survival. Unfortunately, the major mode of failure leading to poor outcome for retroperitoneal liposarcoma is intra-abdominal locoregional recurrence. The cause for the high rate of local recurrence following resection of retroperitoneal liposarcomas in contrast to limb sarcoma is customarily attributed to the specific anatomical site, containing vital neural and vascular structures, axial skeleton, and visceral organs limiting the ability to perform a wide resection. In addition, inherent tumor biology of liposarcomas has to be considered. The biological behavior of retroperitoneal liposarcomas are unpredictable. Clinically, some well-differentiated (WD) RPS behave in an indolent fashion over many years and never develop a dedifferentiated (DD) component. Other DD RPS develop de novo without a documented WD component. Some WD RPS can recur with a mainly DD component and vice versa. Although WD and DD RPS have a common genetic feature associated with genomic amplification which include amplification in 12q13–15 resulting in *MDM2* and *CDK4* overexpression, the specific genetic and molecular events leading to the unpredictable behavior is still not clear.¹

There is an ongoing debate among specialist sarcoma surgeons regarding what constitutes optimal surgery for RPS; weighing up the possible oncological benefit of a radical multivisceral en bloc resection with possible

increased early and late morbidity while keeping in mind the influence such radical surgery might or might not have on the inherent natural biology of the disease.^{2,3} In this issue, Pollock et al.⁴ describe the patterns of recurrence following surgical resection of retroperitoneal liposarcoma, classifying patterns of recurrence according to tumor number and location in an attempt to correlate patterns of local failure to quality and extent of local therapy and tumor biology. This study expands on previous publications from the same unit on the prognostic value of multifocality in RPS.⁵ As highlighted by the authors, the study has several limitations. As is unfortunately the case in many articles looking at outcomes for RPLS, data were extracted retrospectively from dictated operative reports, and included primary RPLS as well as recurrent RPLS patients who had their primary treatment performed elsewhere. It must be kept in mind that the patient population undergoing surgical treatment for recurrent RPLS is usually a selected favorable group (i.e. long disease-free interval with better inherent tumor biology) from a greater population of patients with recurrent disease. Notwithstanding these shortcomings, a novel approach to classify patterns of locoregional disease is proposed, characterizing recurrence by tumor number and location. The retroperitoneal cavity is divided into eight compartments with distinct anatomical boundaries. The scoring system is somewhat limited as a two-dimensional instrument to classify tumor recurrence in a three-dimensional field. It must be kept in mind that these usually large tumors occurring in the retroperitoneal space can cause significant anatomical distortion and that the organs forming the three-dimensional tumor margins can differ according to where the tumor develops.³ The organs can also be completely displaced out of their normal anatomical location by tumor. The anterior margin is usually the ipsilateral colon and mesocolon, pancreas, duodenum, liver, or stomach. For right-sided tumors, the terminal ileum and mesentery often

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forms the antero-medial border at the inferior aspect of the tumor. The posterior margin is generally formed by the posterior abdominal wall muscles, iliopsoas muscle, and diaphragm. Depending on where the tumor develops, the kidney can be part of the posterior, superior, or anterior margin, or can be encased by the tumor. The great vessels, paraspinous muscles, and spine usually form the medial margins, but large tumors often cross the midline and reach the contralateral bowel/mesentery which then serve as the medial margin. This significant variability in initial presentation and involvement of different organs serving as a margin in a three-dimensional model, makes reliable classification of recurrence difficult when the information regarding initial margins is obtained in a retrospective fashion. Prospectively collected data recording the margins at risk during primary surgery should provide more reliable outcome data at the time of recurrence. To characterize the number of tumors, unifocal disease is defined as the presence of one solitary tumor, and multifocal disease is defined as the presence of two or more non-contiguous tumors. It must be kept in mind that liposarcoma can be large heterogeneous tumors, with multiple areas of higher density contained within a single mass of lower density, low-grade liposarcoma. The areas of higher density may represent a focus of DD liposarcoma or subtypes of WD liposarcoma (i.e. sclerosing or inflammatory). This is still classified and should be treated as unifocal disease and not multifocal tumors. Multicentric disease is defined as two or more synchronous tumors in remote, non-contiguous compartments. Outside-field recurrence is defined as the development of a recurrent tumor in a compartment remote from the index tumor at the time of resection.

The authors report that among patients with initial unifocal disease, 57 % progressed to multifocal locoregional disease with subsequent recurrence, including 11 % with recurrent tumors outside of the original resection field. No clinicopathological or treatment-related variable, including the type or extent of resection, was predicative of either multifocal or outside-field recurrence. Based on the results, the authors raise awareness of the well documented phenomenon of multifocal and multicentric locoregional recurrence. The authors caution against radical complete compartmental resection (CCR) or liberal visceral resection which may not influence the pattern of recurrence, and postulate that a 'field change' of the retroperitoneal and intra-abdominal fat may contribute to the pattern of recurrence. However, it must be noted that no patient in this series underwent CCR and therefore this report on patterns of locoregional recurrence cannot be extrapolated to centers where CCR are now performed for the majority of RPS. Another possible explanation for the pattern of recurrence could be that multifocal or multicentric and even out-of-field recurrence can be caused by tumor cells

seeded at the primary operation, or caused by residual microscopic disease which remained on surrounding viscera when a 'simple tumor resection' without adjacent viscera resection was performed. The concept of a 'field change' in the intra-abdominal fat may surely play a role in some of the recurrences described and is a concept that needs further investigation by prospective collection and biobanking of not only RPS tumor samples but also normal retroperitoneal and intra-abdominal fat to further develop the existing knowledge regarding adipogenesis and liposarcomagenesis. Having these primary samples available for genomic and specific RNA expression profiling when a patient undergoes resection of a future recurrent tumor can shed light on whether recurrent disease are due to residual tumor which remained after initial resection, or due to the development of *de novo* lesions in an area of field change. Clinically, the establishment of a multicenter, collaborative, prospective database capturing clinical, operative, histopathology, and radiological information, and recording patterns of recurrence, is strongly supported.

COMPLETE COMPARTMENTAL RESECTION OUTCOMES

The concept of CCR has caused much debate in recent years.^{6,7} The surgical concept advocated is a policy of more liberal visceral en bloc resection of RPS to include an envelope of normal tissue/uninvolved adjacent organs around the tumor to minimize the risk of microscopic positive margins in the hope of improving local control. The technical details have been published by an international panel of sarcoma surgeons who described how RPS might be approached in order to set a standardized surgical strategy.⁸ This approach was in contrast to past recommendations advocating a surgical policy, with the principal aim being gross complete resection and where the need for adjacent organ resection was limited to unequivocal direct tumor involvement. There remains significant controversy regarding the benefit and associated morbidity of multi-visceral resection; however, reported short-term morbidities are in line with most other reported series reporting on outcomes of RPS.⁹ Prospective data on short- and long-term morbidities, oncological outcomes, and quality of life comparing these two surgical strategies are urgently needed. Reported oncological results are very promising. It is difficult to directly compare oncological outcomes between different treatment centers, and confounding factors include selection of patients where surgery is able to achieve an R0/R1 resection, inclusion of primary and recurrent disease, different tumor grade and subtypes included in studies, different surgical and adjuvant strategies, and difference in time and method of

follow-up. However, the local recurrence rate in this series is very high compared with reported European series from centers where CCR are performed regularly.^{9,10} In this current series, when looking exclusively at the primary RPS group with unifocal disease, the local recurrence rate is 68 % (64/94 patients), with a median follow-up of 47 months. Two recently reported European series^{9,10} of primary RPS report local recurrence rates of 19 % ($n = 48/249$ patients; follow-up 37 months) and a 5-year LR rate of 21 % ($n = 136$ patients; follow-up 48 months), respectively. Benefit in these series was specifically seen in Grade 1–2 tumors, while distant metastasis were a limiting factor in high-grade RPS. Divergent surgical approaches may certainly explain some of the differences seen in locoregional recurrence rates between units.

During surgical resection of sarcomas, complete resection with histologically confirmed circumferential negative margins provides the best chance of long-term, local recurrence-free survival. However, microscopic negative margins may not be realistic to achieve in many patients, or practical to evaluate circumferentially in large retroperitoneal tumors. Although R0 resection is the ultimate aim in curative resection for limb sarcoma, the practicality and reproducibility of this in the retroperitoneum is questioned. Due to the usually large tumors occurring in a complex anatomical space surrounded by vital structures, axial skeleton, and visceral organs, wide microscopically clear margins are often difficult or impossible to achieve and many patients are left with positive resection margins. However, histologically confirmed microscopic negative margins should remain the goal at resection, but may be challenging to achieve and difficult to evaluate.³ The issue whether surgical quality and R0 status is operator-dependent or tumor biology-driven, and the relative contribution of these prognostic factors on outcome, will remain an ongoing debate. It is important to remember that margin status is the only potentially surgically-modifiable factor that can be optimized to offer the patient the best chance of cure. This may require liberal visceral en bloc resection of easily disposable adjacent organs to improve the quality of margins along some surfaces while performing a marginal but complete excision along critical structures. The evidence from limb sarcoma surgery demonstrate the concept of limited marginality.¹² A resection with a planned close or positive margin over a critical structure, but negative in all other dimensions, is definitely better than a marginal resection in all dimensions of the tumor. This may become even more important with the increased use of preoperative radiotherapy in RPS, with radiotherapy delivered to include and focus on margins identified to be at risk.

The authors advocate that the kidney should be preserved whenever possible, despite most RPS lying in close relation to the kidney and many arise in the peri-renal fat.

The reasoning behind this is for patients to better tolerate nephrotoxic ifosfamide-based chemotherapy should they develop unresectable or distant disease in the future. It must be noted that ifosfamide-based chemotherapy treatment is not associated with an overall survival benefit in either the adjuvant or palliative setting.¹¹ It should be considered with caution to preserve the kidney whenever possible, as this may compromise the quality of local treatment during the first operation in order to facilitate potentially systemic treatment which has no overall survival benefit. The first operation, which is the best opportunity to perform the only operation which may determine the ultimate outcome. Performing a piecemeal or R2 resection should be strongly discouraged, even though in this study it did not predict patterns of locoregional recurrence. Macroscopic complete resection without tumor rupture remains the principal surgical treatment for all sarcomas, including retroperitoneal sarcomas. En bloc resection should be planned to include adherent organs and structures to improve the chance of achieving a microscopically clear margin. Judgment must be used in deciding which adjacent viscera and vital structures to sacrifice, considering the potential for local control and long-term survival, but balanced against the inherent tumor biology and surgical morbidity of extended resections.

The most important change in surgical oncology has been the concept of concentrating rare and complex operations in high-volume specialist centers leading to improved short- and long-term outcomes. Strong evidence also exists to demonstrate better outcomes for RPS managed in centralized multidisciplinary specialist centers.^{7,13,14} The multidisciplinary team that makes management decisions should include a surgeon with specialized training in resection of RPS, with an understanding and recognition of the biologic behaviour, response to different treatment and clinical outcomes according to histological subtype. Sarcoma surgeons in specialist high-volume centers should have specific anatomical knowledge of the retroperitoneal space, and develop skills and experience to better select patients where a complete resection would be possible, better judgment to determine the extent of organ resection required to obtain complete resection, and develop skills to be more comfortable with performing a complex multivisceral en bloc resection. In specialist sarcoma units, patients will have the opportunity to be considered for international collaborative prospective trials and entry into a prospective database. To ensure the optimal outcome for every patient with an RPS, countries should develop a national strategy to concentrate treatment within specialist sarcoma centers.

CONFLICTS OF INTEREST The authors indicate no potential conflicts of interest.

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