Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Retroperitoneal Sarcoma

Introduction

Sarcoma is a rare type of cancer that develops in the connective tissues, Connective tissues include: muscle, bone, nerves, cartilage, tendons, blood vessels including fatty and fibrous tissues.

Soft tissue sarcomas are a group of rare tumours that together make up only 1 percent of all adult cancers. Although these tumours can occur anywhere in the body, about 20 percent (0.2 percent of all cancers) develop in the back of the abdomen, next to the kidneys, in a relatively "hidden" location known as the retroperitoneum. Here, retroperitoneal sarcomas grow slowly over time and, in fact, once detected, are typically 20 to 30 centimetres, quite possibly the largest tumours in the human body. But aside from their visually shocking giant size, retroperitoneal sarcomas are among the most challenging cancers to treat.

Retroperitoneal Sarcoma (RPS)

Retroperitoneal sarcomas occur in the retroperitoneum. The retroperitoneum is an area behind the peritoneum. The peritoneum is the lining of the abdominal space that covers all of the abdominal organs.

The retroperitoneum is deep in the abdomen and pelvis, behind the abdominal lining, where organs such as the major blood vessels, kidneys, pancreas and bladder are located.

The main types of sarcoma that occur in the retroperitoneum are:

- Liposarcoma – sarcoma of fatty tissue
- Leiomyosarcoma – sarcoma of involuntary muscle
- Other less common types of sarcoma that can occur in the retroperitoneum include:
  - solitary fibrous tumour
  - pleomorphic sarcoma
  - malignant nerve sheath tumour
  - synovial sarcoma
  - Ewing's sarcoma

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Incidence of Retroperitoneal Sarcoma in South Africa

The South African National Cancer Registry (2016) does not provide any information regarding the incidence of Retroperitoneal Sarcoma.

Signs and Symptoms of Retroperitoneal Sarcoma

Often, Retroperitoneal Sarcoma (RPS) manifests with vague, indolent symptoms that present a diagnostic challenge or is discovered incidentally on imaging.

Diagnosis and Grading of Retroperitoneal Sarcoma

Retroperitoneal Sarcoma (RPS) manifests with vague, indolent symptoms that present a diagnostic challenge or is discovered incidentally on imaging. Adequate, detailed imaging of the retroperitoneum with good visualization of the tumour and its relationship with adjacent organs and their potential involvement is critical. Contrast-enhanced CT of the abdomen and pelvis is often sufficient for the diagnosis of RPS. This imaging modality also provides a good indication of the nature of the tumour and is ideal for biopsy planning. A CT scan of the chest is then sufficient to complete staging in most cases. Magnetic resonance imaging can be used in patients with allergies to intravenous contrast as well as in cases in which an assessment of spinal/vertebral foramina, nerves, and/or posterior muscles involvement is necessary.

Mcaddy, N.C., Hallin, M., Strauss, D., Smith, M., Hayes, A., Yusuf, S., Moskovic, E., Fotiadis, N., van Houdt, W., Jones, R.L., Gronchi, A., Thway, K. & Messiou, C. 2019.

BACKGROUND: Initial grading of retroperitoneal leiomyosarcoma (LMS) is performed by core biopsy (CB) however, discrepancy between grade of tumour at initial CB and surgical excision is recognised, raising concerns about the accuracy of CB for directing neoadjuvant therapy. The histological grading system used for staging LMS consists of 3 components: tumour differentiation, mitotic index and proportion of necrosis. We postulate that assessment of necrosis by histopathology alone is inadequate, resulting in under-grading of LMS. We propose and assess a combined grading system that incorporates CT scan findings into pre-surgical grading.

METHODS: Retrospective, blinded review of CT, CB histology and final surgical histology of patients with retroperitoneal LMS was undertaken. A modified grading system, $_{CT}$H-Grade, was derived by replacing the CB necrosis score with a CT-derived necrosis score. The sensitivity and specificity of $_{CT}$H-Grade, the standard histopathology scoring, H-grade were compared. Inter-observer variability in assessment of CT necrosis was also assessed.

RESULTS: 53 patients fulfilled criteria for inclusion. CT was more sensitive at detection of necrosis than CB histology alone with sensitivity of 100% vs 53%. The use of $_{CT}$HGrade resulted in increased detection of high-grade tumours with $_{CT}$H-grade having sensitivities of 80% and 35% for Grade 2 and 3 tumours respectively vs 53% and 15% with H-Grade. Assessment of reader agreement demonstrated Kappa scores of 0.8.

CONCLUSION: Histology from CB under-grades LMS due to undersampling of tumour necrosis. CT is more sensitive in assessing necrosis and its incorporation into a modified CT-histopathology grading system ($_{CT}$H-Grade) improves accuracy of grading with significant implications for patient management.

Treatment of Retroperitoneal Sarcoma

Complete surgical resection with negative margins remains the cornerstone of treatment of nonmetastatic Retroperitoneal Sarcoma (RPS) and is the only chance for cure. In order to achieve negative margins, multivisceral *en bloc* resection is often necessary.

Radiation therapy (RT) has long been an important tool in the multimodal treatment of this disease. There has been great debate, however, over the use of radiation therapy.

Bonvalot, S., Gronchi, A., Le Péchoux, C., Swallow, C.J., Strauss, D., Meeus, P., van Coevorden, F., Stoldt, S., Stoeckle, E., Rutkowski, P., Rastrelli, M., Raut, C.P., Hompes, D., De Paoli, A., Sangalli, C., Honoré, C., Chung, P., Miah, A., Blay, J.Y., Fiore, M., Stelmes, J.J., Dei Tos, A.P., Baldini, E.H., Litière, S., Marreaud, S., Gelderblom, H. & Haas, R.L. 2020.

Background: Unlike for extremity sarcomas, the efficacy of radiotherapy for retroperitoneal sarcoma is not established. The aim of this study was to evaluate the impact of preoperative radiotherapy plus surgery versus surgery alone on abdominal recurrence-free survival.

Methods: EORTC-62092 is an open-label, randomised, phase 3 study done in 31 research institutions, hospitals, and cancer centres in 13 countries in Europe and North America. Adults (aged ≥18 years) with histologically documented, localised, primary retroperitoneal sarcoma that was operable and suitable for radiotherapy, who had not been previously treated and had a WHO performance status and American Society of Anesthesiologists score of 2 or lower, were centrally randomly assigned (1:1), using an interactive web response system and a minimisation algorithm, to receive either surgery alone or preoperative radiotherapy followed by surgery. Randomisation was stratified by hospital and performance status. Radiotherapy was delivered as 50·4 Gy (in 28 daily fractions of 1·8 Gy) in either 3D conformal radiotherapy or intensity modulated radiotherapy, and the objective of surgery was a macroscopically complete resection of the tumour mass with en-bloc organ resection as necessary. The primary endpoint was abdominal recurrence-free survival, as assessed by the investigator, and was analysed in the intention-to-treat population. Safety was analysed in all patients who started their allocated treatment. This trial is registered with ClinicalTrials.gov, NCT01344018.

Findings: Between Jan 18, 2012 and April 10, 2017, 266 patients were enrolled, of whom 133 were randomly assigned to each group. The median follow-up was 43·1 months (IQR 28·8-59·2). 128 (96%) patients from the surgery alone group had surgery, and 119 (89%) patients in the radiotherapy and surgery group had both radiotherapy and surgery. Median abdominal recurrence-free survival was 4·5 years (95% CI 3·9 to not estimable) in the radiotherapy plus surgery group and 5·0 years (3·4 to not estimable) in the surgery only group (hazard ratio 1·01, 95% CI 0·71-1·44; log rank p=0·95). The most common grade 3-4 adverse events were lymphopenia (98 [77%] of 127 patients in the radiotherapy plus surgery group vs one [1%] of 128 patients in the surgery alone group), anaemia (15 [12%] vs ten [8%]), and hypoalbuminaemia (15 [12%] vs five [4%]). Serious adverse events were reported in 30 (24%) of 127 patients in the radiotherapy plus surgery group, and in 13 (10%) of 128 patients in the surgery alone group. One (1%) of 127 patients in the radiotherapy plus surgery group died due to treatment-related serious adverse events (gastropleural fistula), and no patients in the surgery alone group died due to treatment-related serious adverse events.

Interpretation: Preoperative radiotherapy should not be considered as standard of care treatment for retroperitoneal sarcoma.

Funding: European Organisation for Research and Treatment of Cancer, and European Clinical Trials in Rare Sarcomas.

Willis, F., Schimmack, S., Uhl, M., Haefner, M.F., Mechtersheimer, G., Hinz, U., Schmidt, T., Debus, J., Fröhling, S. & Schneider, M. 2020 .

Introduction: In retroperitoneal soft tissue sarcoma (STS) local recurrence (LR) rates remain high despite more aggressive surgical approaches. Since wide resection margins cannot be achieved in all patients,

application of intraoperative radiation therapy (IORT) has been frequently discussed. Still, the significance of IORT in multimodal treatment of retroperitoneal STS remains unclear.
Material and methods: Patients undergoing resection of primary or recurrent retroperitoneal STS at the University of Heidelberg Department of General, Visceral and Transplantation Surgery were retrospectively analyzed. Univariate Kaplan-Meyer and multivariate Cox regression analyses were performed to identify predictors of LR-free survival and to investigate the impact of IORT and high cumulative radiation doses. Analyses with propensity-score matched subgroups for IORT and cumulative radiation dose were performed to control for selection bias. Subgroup analyses for patients with retroperitoneal liposarcoma were likewise performed.
Results: 272 patients were identified. Recurrent tumors, histology of dedifferentiated liposarcoma or unclassified sarcoma and microscopically incomplete resection were associated with decreased LR-free survival. In liposarcoma, only recurrent and dedifferentiated tumors were confirmed as poor prognostic factors concerning LR. IORT and cumulative radiation doses exceeding 60 Gy did not influence LR rates (estimated 5-year LR-free survival: IORT: 39%, non-IORT: 46%; p = 0.79).
Conclusion: In this retrospective evaluation, additional application of IORT does not significantly influence oncological outcome in retroperitoneal soft tissue sarcoma. Randomized trials are needed to clarify the benefit of IORT.

Herzberg, J., Niehaus, K., Holl-Ulrich, K., Honarpisheh, H., Guraya, S.Y. & Strate, T. 2019.
"Retroperitoneal liposarcomas are a heterogeneous group of mesenchymal tumours that have a wide spectrum of histological subtypes and vague clinical presentations. Herein, we present the case of a 75-year-old man with anorexia, weight loss of 7 kg, and a growing abdominal circumference within a span of 6 weeks. Computed tomography of the abdomen and pelvis showed a large mass that filled almost the entire abdominal cavity. After consultation with a multidisciplinary tumour board, en bloc resection of the tumour was performed. In addition, the left kidney and a part of the left diaphragm were removed. The tumour measured 35 × 29 × 20.5 cm and weighed 11.6 kg. The histological report confirmed low-grade dedifferentiated liposarcoma with scarce atypical adipocytes, lipoblasts containing spindle cell, pleomorphic, and chondroid components. The patient had uneventful recovery and remained stable during the follow-up period. We report this case to highlight the need for customized surgical oncological measures in the treatment of solid abdominal tumours due to locoregional invasion that usually necessitates en bloc resection."

Asencio, P.J.M., Fernandez, H.J.A., Blanco, F.G., Muñoz, C.C., Álvarez, Á.R., Fox, A.B., Lozano, B.A., Rodriguez, B.M., Cantin, B.S. & Artigas, R.V. 2019.
"Surgery for retroperitoneal sarcomas should be "en bloc" compartmental, which involves resection of unaffected organs. Its upfront use is key, providing a high percentage of resections with negative margins, resulting in a better local control and increased survival in many patients. Preservation of organs should be done in an individualized manner, especially in the pelvic location, and adapted to the histological aggressiveness of the tumor. Preoperative biopsy is able to establish the diagnosis of sarcoma subtype and consequently an adequate perioperative strategy. These patients should be managed by expert surgeons at referral centers with multidisciplinary units and oncology committees. The use of chemotherapy and radiotherapy is not yet well defined, so it is only recommended at referral centers with clinical trials. Currently, this is the only option to offer the best morbidity and mortality rates, as well as possible improvements in the survival of these patients."

Chouliaras, K., Senehi, R., Ethun, C.G., Poultsides, G., Grignol, V., Clarke, C.N., Roggin, K.K., Fields, R.C., Schwartz, P.B., Ronnekleiv-Kelly, S.M., D'Agostino, R. Jr., Johnson, E.N., Levine, E.A., Cardona, K. & Votanopoulos, K.I. 2019.

BACKGROUND: The use of radiation therapy in the treatment of retroperitoneal sarcomas has increased in recent years. Its impact on survival and recurrence is unclear.
METHODS: A retrospective propensity score matched (PSM) analysis of patients with primary retroperitoneal soft tissue sarcomas, who underwent resection from 2000 to 2016 at eight institutions of the US Sarcoma Collaborative, was performed. Patients with metastatic disease, desmoid tumors, and palliative resections were excluded.
RESULTS: Total 425 patients were included, 56 in the neoadjuvant radiation group (neo-RT), 75 in the adjuvant radiation group (adj-RT), and 294 in the no radiotherapy group (no-RT). Median age was 59.5 years, 186 (43.8%) were male with a median follow up of 31.4 months. R0 and R1 resection was achieved in 253 (61.1%) and 143 (34.5%), respectively. Overall 1:1 match of 46 adj-RT and 59 neo-RT patients was performed using histology, sex, age, race, functional status, tumor size, grade, resection status, and chemotherapy. Unadjusted recurrence-free survival (RFS) was 35.9 months (no-RT) vs 33.5 months (neo-RT) and 27.2 months (adj-RT), P = .43 and P = .84, respectively. In the PSM, RFS was 17.6 months (no-RT) vs 33.9 months (neo-RT), P = .28 and 19 months (no-RT) vs 27.2 months (adj-RT), P = .1.
CONCLUSIONS: Use of radiotherapy, both in adjuvent or neoadjuvent setting, was not associated with improved survival or reduced recurrence rate.

Transatlantic Australasian Retroperitoneal Sarcoma Working Group. 2019.
BACKGROUND: Schwannomas are rare tumours that pose a significant management challenge in the abdomen, retroperitoneum and pelvis. No data are available to inform management strategy.
METHODS: A collaborative international cohort study, across specialist sarcoma units, was conducted to include adults presenting between 2000 and 2017 with histopathologically confirmed schwannomas within the abdomen, retroperitoneum or pelvis.
RESULTS: Of 485 patients across 12 centres, 38 (7·8 per cent) were discharged without follow-up, 199 (41·0 per cent) underwent early resection and 248 (51·1 per cent) had radiological monitoring. Of these 248 patients, 96 (38·7 per cent) eventually had surgery, giving an overall resection rate of 60·8 per cent (295 of 485). At baseline, median tumour volume was 90·1 (i.q.r. 26·5-262·0) cm^3 . The estimated growth rate was 10·5 (95 per cent c.i. 9·4 to 11·6) per cent per year, and was consistent in the short term (within 2 years of diagnosis) and long term (beyond 2 years) (ρ = 0·405, P = 0·021). A decision to operate was more common in symptomatic patients (P < 0·001) and for rapidly growing tumours (growth rate more than 20 per cent per year) (P = 0·025). R0/R1 resection was achieved in 91·6 per cent of patients (263 of 287). Kaplan-Meier long-term recurrence rates after R0/R1 resection were 2·3 and 6·7 per cent at 3 and 5 years respectively.
CONCLUSION: Specific recommendations include: indications for early surgery, prediction of growth from radiological monitoring, promotion of selective submacroscopic resection and cessation of postoperative imaging surveillance.

Recurrence of Retroperitoneal Sarcoma
Retroperitoneal sarcoma can reappear in the same area after the treatment for a previous tumour; this is called a local recurrence. It can also come back near the site of the first tumour or spread through to the abdomen. If the sarcoma does reappear, it is important to get treated as quickly as possible. It is useful to check for recurrences through self-examination: as the treating physician what to look for.

The sarcoma can also spread to another part of the body. This is called metastasis. In retroperitoneal sarcoma patients, 'metastases may appear in the lungs, which is why a chest x-ray is usually taken at follow-up appointments.

Treatment for secondary sarcoma may involve surgery, radiotherapy or chemotherapy as appropriate. Treatment is usually assessed on an individual basis.

Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). 2018.
Introduction: Retroperitoneal sarcoma (RPS) is a rare disease accounting for 0.1%–0.2% of all malignancies. Management of RPS is complex and requires multidisciplinary, tailored treatment strategies at all stages, but especially in the context of metastatic or multifocal recurrent disease. Due to the rarity and heterogeneity of this family of diseases, the literature to guide management is limited.
Methods: The Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG) is an international collaboration of sarcoma experts from all disciplines convened in an effort to overcome these limitations. The TARPSWG has compiled the available evidence surrounding metastatic and multifocally recurrent RPS along with expert opinion in an iterative process to generate a consensus document regarding the complex management of this disease. The objective of this document is to guide sarcoma specialists from all disciplines in the diagnosis and treatment of multifocal recurrent or metastatic RPS.
Results: All aspects of patient assessment, diagnostic processes, local and systemic treatments, and palliation are reviewed in this document, and consensus recommendations provided accordingly. Recommendations were guided by available evidence, in conjunction with expert opinion where evidence was lacking.
Conclusions: This consensus document combines the available literature regarding the management of multifocally recurrent or metastastic RPS with the practical expertise of high-volume sarcoma centers from multiple countries. It is designed as a tool for decision making in the complex multidisciplinary management of this condition and is expected to standardize management across centers, thereby ensuring that patients receive the highest quality care.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Medical Disclaimer
This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any

liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted and/or Utilised

Asencio, P.J.M., Fernandez, H.J.A., Blanco, F.G., Muñoz, C.C., Álvarez, Á.R., Fox, A.B., Lozano, B.A., Rodriguez, B.M., Cantin, B.S. & Artigas, R.V. 2019. **Update in pelvic and retroperitoneal sarcoma management: The role of compartment surgery.** *Cir Esp.* 2019 Nov;97(9):480-488. doi: 10.1016/j.ciresp.2019.06.011. Epub 2019 Sep 12. English, Spanish.

Bonvalot, S., Gronchi, A., Le Péchoux, C., Swallow, C.J., Strauss, D., Meeus, P., van Coevorden, F., Stoldt, S., Stoeckle, E., Rutkowski, P., Rastrelli, M., Raut, C.P., Hompes, D., De Paoli, A., Sangalli, C., Honoré, C., Chung, P., Miah, A., Blay, J.Y., Fiore, M., Stelmes, J.J., Dei Tos, A.P., Baldini, E.H., Litière, S., Marreaud, S., Gelderblom, H. & Haas, R.L. 2020. Preoperative radiotherapyplus surgery versus surgery alone for patients withprimary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020 Oct;21(10):1366-1377.

Chouliaras, K., Senehi, R., Ethun, C.G., Poultsides, G., Grignol, V., Clarke, C.N., Roggin, K.K., Fields, R.C., Schwartz, P.B., Ronnekleiv-Kelly, S.M., D'Agostino, R. Jr., Johnson, E.N., Levine, E.A., Cardona, K. & Votanopoulos, K.I. 2019. Role of radiation therapy for retroperitoneal sarcomas: An eight-institution study from the US Sarcoma Collaborative. *J Surg Oncol*. 2019 Dec;120(7):1227-1234. doi: 10.1002/jso.25694. Epub 2019 Sep 4.

Herzberg, J., Niehaus, K., Holl-Ulrich, K., Honarpisheh, H., Guraya, S.Y. & Strate, T. 2019. Giant retroperitoneal liposarcoma: a case report and literature review. *Talbah Univ Med Sci*. 2019 Oct 11;14(5):466-471. doi: 10.1016/j.jtumed.2019.08.005. eCollection 2019 Oct.

Mcaddy, N.C., Hallin, M., Strauss, D., Smith, M., Hayes, A., Yusuf, S., Moskovic, E., Fotiadis, N., van Houdt, W., Jones, R.L., Gronchi, A., Thway, K. & Messiou, C. 2019. CT imaging improves histopathological grading or retroperitoneal leiomyosarcomas. *Eur J Surg Oncol*. 2019 Oct 10. pii: S0748-7983(19)30888-1. doi: 10.1016/j.ejso.2019.10.007. [Epub ahead of print]

Retroperitoneal Sarcoma
https://sarcoma.org.uk/sarcoma-types/retroperitoneal-sarcoma
https://www.cancernetwork.com/oncology-journal/diagnosis-and-management-retroperitoneal-sarcoma
https://www.curetoday.com/publications/cure/2017/rare-cancer-summer-2017/understanding-retroperitoneal-sarcoma
https://www.uptodate.com/contents/surgical-resection-of-retroperitoneal-sarcoma
https://www.uptodate.com/contents/surgical-resection-of-retroperitoneal-sarcoma
https://jamanetwork.com/journals/jamasurgery/fullarticle/394415
https://www.hindawi.com/journals/sarcoma/2009/605840/
https://www.cancernetwork.com/oncology-journal/diagnosis-and-management-retroperitoneal-sarcoma
https://www.cancernetwork.com/oncology-journal/diagnosis-and-management-retroperitoneal-sarcoma/page/0/1

Transatlantic Australasian Retroperitoneal Sarcoma Working Group. 2019. Intercontinental collaborative experience with abdominal, retroperitoneal and pelvic schwannomas. *Br J Surg*. 2019 Nov 17. doi: 10.1002/bjs.11376. [Epub ahead of print]

Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). 2018. Management of metastatic retroperitoneal sarcoma: a consensus approach from the Trans-Atlantic Retroperitoneal Sarcoma Working Group (TARPSWG). *Annals of Oncology*, Volume 29, Issue 4, 1 April 2018, Pages 857–871, https://doi.org/10.1093/annonc/mdy052.

Van Houdt, W.J., Zaidi, S., Messiou, C., Thway, K., Strauss, D.C. & Jones, R.L. 2017. Treatment of retroperitoneal sarcoma: current standards and new developments. Current Opinion in Oncology: July 2017 - Volume 29 - Issue 4 - p 260–267. doi: 10.1097/CCO.0000000000000377. SARCOMAS: Edited by Jean-Yves Blay

Willis, F., Schimmack, S., Uhl, M., Haefner, M.F., Mechtersheimer, G., Hinz, U., Schmidt, T., Debus, J., Fröhling, S. & Schneider, M. 2020 . Significance of intraoperative radiation therapy and high cumulative radiation doses in retroperitoneal soft tissue sarcoma. *Eur J Surg Oncol*. 2020 May;46(5):905-913.