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The role of standard and novel radiotherapy approaches in management of retroperitoneal sarcomas

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ABSTRACT

Primary non-metastatic retroperitoneal soft tissue sarcoma patients can be cured by radical surgery. However there remains a risk for patients to develop a local recurrence. To minimize this risk, patients with low grade liposarcomas might benefit from preoperative radiotherapy. This review summarizes all issues that should be considered for the irradiation of patients with retroperitoneal soft tissue sarcoma.

1. Introduction

In the past decade, several initiatives have substantially helped in building our knowledge concerning retroperitoneal sarcomas (RPS). Retrospective analyses of large databases have been published. First, Nussbaum et al., have retrospectively searched the National Cancer Data Base and have reported on the oncological outcomes in 9068 patients, suggesting an improved overall survival by the addition of radiotherapy to surgery [1]. Second, Gronchi, leading the TransAtlantic RetroPeritoneal Sarcoma Working Group (TARPSWG), presented insight into the clinical behavior of different subtypes in their 1007 RPS patient database [2]. The only prospective clinical data currently available is derived from the European Organization for Research and Treatment of Cancer – Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) randomized 62092-22092 trial recently reported in the Lancet Oncology [3].

In this special issue, we present our evidence-based view on the role of radiotherapy (RT), (RT) in relation to surgery, the mainstay of treatment, in the setting of RPS. We strive to clarify questions such as “if”, “when” and “how”and highly recommend the referral of patients to specialized RPS centers [4,5].

2. Patient selection for radiation therapy

In the STRASS study (EORTC-62092) 266 patients were randomized between surgery alone and RT followed by surgery [3]. In this trial patients with all prevalent histological RPS subtypes were eligible. Results showed no difference in abdominal recurrence-free survival between the two study arms, leading to the overall conclusion that routinely performed preoperative radiotherapy should not be part of RPS patient management. However, further exploratory analysis of the subgroup of liposarcomas revealed a 10% absolute benefit in abdominal recurrence-free survival by preoperative RT and two times fewer local recurrences [3]. Patients treated in the same accrual period and the same hospitals as STRASS patients, but not included in the trial for several reasons were analyzed as well. This, so called, STREXIT analysis included over 800 RPS patients and showed a 14% increase in local control rate at 3 years after preoperative radiation. especially in patients with primary well-differentiated liposarcoma or G1-2 dedifferentiated liposarcoma [6]. Treatment with RT should also be considered for patients with unresectable RPS. Retrospective analysis of 14 patients showed no progression of disease at 12 months after definitive RT in 10 patients, in 6 patients local control (LC) lasted more than 2 years with no or minimal toxicity [7].

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3. Timing of radiation therapy

The poor outcome of RPS is explained by a relatively high incidence of abdominal recurrences defined as local relapse or peritoneal sarcomatosis. Five years survival rates in intermediate and low-grade RPS are about 50–60% [8]. Multivisceral resection (*i.e.* removal of viscera/organs adjacent to the RPS) is nowadays the gold standard [9]. As opposed to limb sarcoma, adjuvant RT is not a standard and data available on the timing of radiation therapy are derived from retrospective series.

3.1. Preoperative radiotherapy

Already in 2006, Tzeng, conducted a prospective study on a small patients cohort investigating the efficacy and feasibility of selective dose escalation by IORT/BRT on areas at risk. They assessed the impact on local control using two dose levels; one for the entire gross tumour volume and another for the posterior abdominal wall (being the most at risk of local recurrence) by IMRT. At two years the LC was 80% in line with the historical series, but with a low toxicity profile [10]. Delaney pursued the same line of investigations in a phase I dose escalating study by a simultaneous integrated boost by IMRT or intensity modulated proton therapy (IMPT) [11].

As described above, the STRASS trial results showed that the abdominal relapse-free survival was similar in both study arms for the entire population, with an hint of improved outcome in the sensitivity analysis of the liposarcoma subgroup, however, at date of publication, without impact on OS [3]. In the recently published STREXIT results preoperative RT was associated with improved local control in patients with liposarcomas, especially well-differentiated liposarcomas and G1-2 dedifferentiated liposarcomas with a hazard rate of 0.63 (95% CI 0.40–0.97) [6]. The retrospective TARPSWG study by Haas et al. suggested that preoperative RT for well-differentiated liposarcomas and grade I or 2 liposarcomas can be associated with better LC on univariable analyses but not after propensity score-matched analyses [12]. There is growing evidence that preoperative RT is not going to be beneficial for an unselected group of RPS patients comprising all histologic variants of the disease [13].

3.2. Postoperative radiotherapy (PORT)

Retrospective series analyzed the role of PORT in RPS after classical surgery (*i.e.* surgery without resection of the adjacent viscera/organs). PORT seems to reduce the risk of local relapse by a factor 3 [9]. In a large retrospective mono institutional analysis, after multivisceral surgery and adjuvant RT, PORT seemed to reduce abdominal relapses, however, with no impact in terms of overall survival (OS) [14]. Delivery of at least 50Gy in an adjuvant setting was hampered by small bowel presence with a 50% of risk of acute and chronic enteritis [15]. In this French study, the use of spacer to displace the bowel outside the radiation field, was suggested [16]. Another large retrospective study by Nussbaum et al. was published in Lancet Oncology and compared the impact on local control and overall survival of PORT and preoperative RT. Both preoperative RT and PORT were significantly associated with improved OS compared with surgery alone [1].

Furthermore, the use of more sophisticated RT such as intensity modulated RT (IMRT) or volumetric modulated arc therapy (VMAT), both in the pre- and postoperative setting, may also reduce the dose delivered to the small bowel, thereby reducing toxicity [17]. However, in the latest ESMO and ASTRO guidelines, PORT after radical surgery is discouraged since it is difficult to deliver a significant radiation dose without gastrointestinal side effects [13,18].

4. Patient preparation and immobilization

Related to the diversity of clinical scenarios, RT preparation in RPS should be individualized [19]. Planning CT is usually performed in the supine position. The arms must be positioned outside the planned entry and exit of the beams. Thus, if possible, the upper extremities should be positioned above the head by dedicated supports. Optional immobilization devices, such as vacuum bags may be applied if desired. The use of intravenous and oral contrast agents is not mandatory but can be useful in selected cases, for example, to visualize small bowel loops. An alternative approach could be the fusion of the planning CT with contrast-enhanced diagnostic CT or MRI.

The scanning area and motion management techniques should be adapted to the localization, movability, and size of the tumor. Larger tumors require more extensive planning-CT field of view, preferably from the level above the diaphragm to the level of the lesser trochanter. The desired slice thickness is 2–3 mm. Overall, this value should not exceed 5 mm per slice. CT with motion management (e.g.gating and/or, breath-hold techniques) is not obligatory; however, it is highly recommended in tumors localized more superiorly due to the inter- and intrafraction motions of target volumes and organs at risk [20]. There are no specific recommendations for bowel preparation, but selected methods used for RT planning should be maintained before each fraction. In case of RPS located within the pelvic area, it is recommended to implement an institutional protocol regarding bladder and rectal filling during both RT preparation and irradiation.

5. Delineation

5.1. GTV and iGTV

The gross tumor volume (GTV) should be based on a planning CT, preferably supplemented with T1-weighted post-gadolinium MRI sequence. If a 4D-CT scan is available, GTV should be delineated in all breathing phases to create an internal GTV (iGTV).

5.2. CTV and ITV

The clinical target volume (CTV) should cover the GTV or iGTV and surrounding areas at risk for containing microscopic disease. Several RPS RT protocols have described margins as an expansion of the main target volume by 0.5–4 cm. An international sarcoma expert radiation oncology consensus group recommended expansion of the main target volume based on motion management and tumor localization [19]. In case of 4D planning, the internal target volume (ITV) is created by expanding iGTV 1.5 cm isotropically in all directions. Upper abdominal tumors, planned without motion management, require more extensive CTV margins, such as 2–2.5 cm longitudinally and 1.5–2 cm radially. In tumors below the pelvic brim a 1.5 cm symmetrical margin from GTV to CTV is considered satisfactory. After these expansions, the CTV or ITV should be edited manually in the direction of, e.g., uninvolved bowel loops and bony surfaces, to fit the anatomical pattern of tumor spread and avoid unnecessary irradiation of healthy tissues. For example, these manually edited volumes should exclude the retroperitoneal compartment, bones, kidneys, and liver, and should be reduced to about 5 mm in the direction of bowel loops and air cavities, and trimmed 3–5 mm below the skin surface. It is recommended to expand iGTV or GTV 3 cm inferiorly if the tumor extends to inguinal canal. Currently, there are no recommendations regarding CTV in the case of recurrent or unresectable RPS.

5.3. PTV

The Planning Target Volume (PTV) margin depends on tumor size and motion, applied methods of image guidance, used motion management techniques and institutional protocols. Usually, larger margins (9–12 mm) are applied in the case of superiorly located RPS; however, such an extensive PTV may be significantly reduced by the introduction of motion management techniques and daily volumetric image guidance. PTV should consider set-up, calculation, and physical uncertainties as well as organ motion. The recommended expansion from CTV/ITV to PTV is 9–12 mm if no volumetric image guidance will be used. The introduction of frequent (2–5 times per week) volumetric imaging of the tumor and 4D planning may allow significant margin reductions to about 5 mm.

6. Dose and fractionation

Currently, the recommended dose in preoperative RT is 50–50.4 Gy in 1.8–2 Gy fractions.[19,22]Data on dose and fractionation in the postoperative RT are scarce, and due to its associated long-term toxicity profile, should be discouraged even more when considering hypofractionation. [21]. Thus, the decision should be made on an individual basis by an experienced multidisciplinary team. Administration of higher total doses in perioperative RT for RPS is hampered by the large volume of these tumors and adjacent radiosensitive abdominal organs at risk. Clinical studies (either by proton beam therapy, by brachytherapy or by simultaneous integrated boost (SIB) techniques by photon beams), will further clarify the feasibility and efficacy of dose escalation [22]. Whereas toxicity of brachytherapy in the upper abdomen was found unacceptable, the use of intraoperative electron RT seemed to be tolerable and associated with high local control rate [22]. Preliminary data regarding safety and efficacy of perioperative SIB up to the total dose of 66 Gy for high-risk target volume are encouraging; however, these studies are limited by small sample sizes and design (prospective register and retrospective cohort study) [10,23]. Important data on SIB will be provided by the results of the ongoing clinical trial NCT01659203 led by the Massachusetts General Hospital. The investigators assess the efficacy of boosting high-risk volumes to 63 Gy in 28 fractions using both IMRT and IMPT. Another mode of increasing local efficacy of RT is the use of hypofractionation, especially using stereotactic techniques. This concept may be especially useful in the case of unresectable or remaining tumor volumes; however, it needs further investigation [7].

7. Brachytherapy (BRT) and intraoperative radiotherapy (IORT)

In 2014, Smith published an update of the Toronto group experience. They suggested that a postoperative boost by BRT had an impact on LC and OS at two years. Taking long-term gastrointestinal toxicities into account at 5 and 10 years, this advantage became less pronounced. Furthermore, at 10 years after BRT OS was not improved and was significantly associated to unacceptable toxicity [22].

Roeder and co-workers reported the results of one of the largest patient cohorts treated with surgery plus IORT as a boost to the tumor bed or to residual tumor. IORT may allow dose escalation during surgery while sparing organs at risk (like small bowel and ureter) [24]. The authors reported a significant survival benefit for patients treated with preoperative external beam RT (EBRT) and IORT compared to PORT or no EBRT at all. The combination of EBRT and IORT during surgery increased LC in this cohort, indicating that dose escalation may be beneficial with a low toxicity profile as compared to PORT. Neurological side effects were the main late toxicities observed [24]. They concluded IORT to be feasible, if carefully selected and performed by experienced hands.

8. Proton beam and carbon ion therapy

Since RPS are often large at diagnosis with sizes frequently exceeding 15 cm and in proximity to sensitive organs like the spinal cord, liver, bowel and kidney, radiation with protons could be beneficial for RPS patients [25]. A study comparing 3D conformal IMRT and photon therapy and 3D conformal proton beam therapy showed an adequate CTV coverage for all three techniques, but with proton therapy lower doses were delivered to normal tissue, i.e. bowel and kidneys. Also, the total integral radiation dose to the body was lower with protons compared with IMRT and 3D conformal photon therapy [26]. With these lower radiation doses on normal tissue, less late toxicity should be expected using proton beam therapy [25]. The use of carbon ion radiotherapy could lead to less radiation dose in the normal tissue as well. Serizawa et al. studied the use of carbon ion radiotherapy for 24 patients with unresectable RPS and showed acceptable LC rates, without grade 3 gastrointestinal tract toxicities [27].

9. Conclusions

Due to the low incidence of RPS patient's referral to specialized centers is highly recommended. Preoperative RT is not standard of care for an unselected population of patients with all prevalent subtypes of RPS. However, as stated the STREXIT analysis suggested a potential benefit for the addition of radiotherapy in the largest subgroup of well-differentiated and G1-2 dedifferentiated liposarcomas. In general postoperative radiotherapy should not be recommended since it leads to a high level of late gastrointestinal toxicity with the most commonly used radiation techniques. However, definitive RT may be carefully considered in unresectable and progressive RPS. Within the setting of RPS, proton beam therapy merits further investigation.

CRediT authorship contribution statement

L.M. Wiltink: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **M.J. Spalek:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **C. Sangalli:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **R.L. Haas:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

References

[1] Nussbaum DP, Rushing CN, Lane WO, et al. Preoperative or postoperative radiotherapy versus surgery alone for retroperitoneal sarcoma: a case-control, propensity score-matched analysis of a nationwide clinical oncology database. Lancet Oncol 2016;17(7):966–75.
[2] Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS working group. Ann Surg 2016;263(5):1002–9.
[3] Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21(10):1366–77.
[4] Bonvalot S, Gaignard E, Stoeckle E, et al. Survival benefit of the surgical

management of retroperitoneal sarcoma in a reference center: a nationwide study of the French sarcoma group from the NetSarc database. Ann Surg Oncol 2019;26(7):2286–93.
[5] Toulmonde M, Bonvalot S, Méeus P, et al. Retroperitoneal sarcomas: patterns of care at diagnosis, prognostic factors and focus on main histological subtypes: a multicenter analysis of the French Sarcoma Group. Ann Oncol 2014;25(3):735–42.
[6] Callegaro D, Raut CP, Ajayi T, et al. Preoperative radiotherapy in patients with primary retroperitoneal sarcoma: EORTC-62092 trial (STRASS) versus off-trial (STREXIT) results. Ann Surg 2022.
[7] Sobiborowicz A, Spałek MJ, Czarnecka AM, Rutkowski P. Definitive radiotherapy in the management of non-resectable or residual retroperitoneal sarcomas: institutional cohort analysis and systematic review. Cancer Control 2021;28:1073274820983028.
[8] Stoeckle E, Coindre JM, Bonvalot S, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. Cancer 2001;92(2):359–68.
[9] Gronchi A, Miceli R, Allard MA, et al. Personalizing the approach to retroperitoneal soft tissue sarcoma: histology-specific patterns of failure and postrelapse outcome after primary extended resection. Ann Surg Oncol 2015;22(5):1447–54.
[10] Tzeng CW, Fiveash JB, Popple RA, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006;107(2):371–9.
[11] DeLaney TF, Chen YL, Baldini EH, et al. Phase 1 trial of preoperative image guided intensity modulated proton radiation therapy with simultaneously integrated boost to the high risk margin for retroperitoneal sarcomas. Adv Radiat Oncol 2017;2(1):85–93.
[12] Haas RLM, Bonvalot S, Miceli R, et al. Radiotherapy for retroperitoneal liposarcoma: a report from the transatlantic retroperitoneal sarcoma working group. Cancer 2019;125(8):1290–300.
[13] Gronchi A, Miah AB, Dei Tos AP, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol 2021;32(11):1348–65.
[14] Le Péchoux C, Musat E, Baey C, et al. Should adjuvant radiotherapy be administered in addition to front-line aggressive surgery (FAS) in patients with primary retroperitoneal sarcoma? Ann Oncol 2013;24(3):832–7.
[15] Letschert JG, Lebesque JV, Aleman BM, et al. The volume effect in radiation-related late small bowel complications: results of a clinical study of the EORTC Radiotherapy Cooperative Group in patients treated for rectal carcinoma. Radiother Oncol 1994;32(2):116–23.
[16] White JS, Biberdorf D, DiFrancesco LM, Kurien E, Temple W. Use of tissue expanders and pre-operative external beam radiotherapy in the treatment of retroperitoneal sarcoma. Ann Surg Oncol 2007;14(2):583–90.
[17] Bossi A, De Wever I, Van Limbergen E, Vanstraelen B. Intensity modulated radiation-therapy for preoperative posterior abdominal wall irradiation of retroperitoneal liposarcomas. Int J Radiat Oncol Biol Phys 2007;67(1):164–70.
[18] Salerno KE, Alektiar KM, Baldini EH, et al. Radiation therapy for treatment of soft tissue sarcoma in adults: executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol 2021;11(5):339–51.
[19] Baldini EH, Wang D, Haas RL, et al. Treatment guidelines for preoperative radiation therapy for retroperitoneal sarcoma: preliminary consensus of an international expert panel. Int J Radiat Oncol Biol Phys 2015;92(3):602–12.
[20] Wong P, Dickie C, Lee D, et al. Spatial and volumetric changes of retroperitoneal sarcomas during pre-operative radiotherapy. Radiother Oncol 2014;112(2):308–13.
[21] Haas RL, Baldini EH, Chung PW, van Coevorden F, DeLaney TF. Radiation therapy in retroperitoneal sarcoma management. J Surg Oncol 2018;117(1):93–8.
[22] Smith MJ, Ridgway PF, Catton CN, et al. Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: long-term results of a prospective trial. Radiother Oncol 2014;110(1):165–71.
[23] Cosper PF, Olsen J, DeWees T, et al. Intensity modulated radiation therapy and surgery for Management of Retroperitoneal Sarcomas: a single-institution experience. Radiat Oncol 2017;12(1):198.
[24] Roeder F, Alldinger I, Uhl M, et al. Intraoperative electron radiation therapy in retroperitoneal sarcoma. Int J Radiat Oncol Biol Phys 2018;100(2):516–27.
[25] DeLaney TF, Haas RL. Innovative radiotherapy of sarcoma: proton beam radiation. Eur J Cancer 2016;62:112–23.
[26] Swanson EL, Indelicato DJ, Louis D, et al. Comparison of three-dimensional (3D) conformal proton radiotherapy (RT), 3D conformal photon RT, and intensity-modulated RT for retroperitoneal and intra-abdominal sarcomas. Int J Radiat Oncol Biol Phys 2012;83(5):1549–57.
[27] Serizawa I, Kagei K, Kamada T, et al. Carbon ion radiotherapy for unresectable retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys 2009;75(4):1105–10.