review

Perioperative radiotherapy versus surgery alone for retroperitoneal sarcomas: a systematic review and meta-analysis

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Background. There is no clear evidence on whether radiotherapy (RT) improves treatment result in patients with retroperitoneal sarcomas (RPS).

Methods. A systematic literature search was performed using PubMed, Scopus and CENTRAL databases. Data were retrieved from published comparatives studies in patients with RPS undergoing surgery alone or RT plus surgery. The primary endpoints were the 5-year OS and the median OS. The secondary endpoints were the recurrence-free survival (RFS) and the R0-resection rate. Continuous outcomes were calculated by means of weighted mean difference (WMD).

Results. Ten out of 374 articles were analyzed. The median OS and the 5-year survival were significantly increased in patients treated with RT and surgery, compared to patients treated with surgery alone ($p < 0.00001$, $p < 0.001$). Median RFS was significantly increased in patients treated with either preoperative ($p < 0.001$) or postoperative ($p = 0.001$) RT compared to patients that underwent surgery alone. Finally, median R0-resection rate was similar between the two groups ($p = 0.56$).

Conclusion. RT along with radical surgery could be the standard of care in at least a subgroup of patients with RPS.

Key words: soft tissue sarcoma; adjuvant radiotherapy; neoadjuvant radiotherapy

Introduction

Retroperitoneal soft tissue sarcomas (RPS) constitute a rare and quite heterogeneous group of mesenchymal neoplasms that are located in the retroperitoneum and count for less than 10–15% of all soft tissue sarcomas (STSs).[1] With an incidence of approximately 0,5–1 case per 100000, these tumors are most often considered sporadic especially in the absence of a genetic syndrome (Li-Fraumeni syndrome, Gardner's syndrome, familial adenomatous polyposis [FAP], Carney-Stratakis syndrome,

Hereditary retinoblastoma, etc.).[2] Histological subtypes are the well-differentiated liposarcoma (WDLPS), leiomyosarcoma dedifferentiated liposarcoma (DDLPS), undifferentiated pleomorphic sarcoma, solitary fibrous tumors, malignant peripheral nerve sheath tumors and synovial sarcoma.[3]

Until now surgery with curative intent (R0 resection) remains the gold standard treatment for most patients with resectable disease contributing to long-term disease-free survival (DFS).[4,5] However, complete macroscopic surgical resection

is achieved in about 70% of the patients reflecting the high incidence of local recurrence and disease progression.[6,7] Thus, multimodality treatment involving RT and/or chemotherapy could favor the ability to obtain negative surgical margins with a subsequently better local control of the disease and longer survival.

Radiotherapy to the retroperitoneum is a quite complex procedure and can be administered pre-operatively, postoperatively, intraoperatively or even in a combined therapy setting. In the era of newer RT techniques as 3D-CRT and IMRT, the surrounding normal tissues can be protected and acute radiation induced adverse events can be reduced.[5]

While current literature is not clear on whether RT, either preoperatively or postoperatively, reflects on a beneficial result in patients with RPS, we aim to investigate if the combination of perioperative RT and surgical resection benefits the overall survival (OS) and the local control of the disease.

Methods

Search strategy and articles selection

The present meta-analysis was performed according to a protocol, which was agreed by all participating authors, along with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[8] A thorough literature search was performed in PubMed (Medline), Scopus (ELSEVIER), and the Cochrane Central Register of Controlled Studies (CENTRAL) databases (last search: October 25, 2018). The following terms were used in every possible combination: "radiotherapy", "radiation therapy", "surgery", "surgical resection", "retroperitoneal sarcoma". The inclusion criteria were: (i) articles with ≥ 10 patients, (ii) English language, (iii) published from 1990 to 2018, and (iv) human subjects. Two independent investigators (AD, DEM) extracted the available data. Any discrepancies regarding the inclusion and/or exclusion of studies were discussed with the guarantor author (KT) until consensus was reached. Moreover, the kappa coefficient test was used in order to evaluate the level of agreement between the reviewers.

Data extraction

Regarding each study that was included, the extracted data was relative to baseline characteristics (sample size for each group, age, sex). The primary endpoints were the 5-year OS and the median OS.

The secondary endpoints were recurrence-free survival and R0 resection rate. Two authors (DEM, FB) performed the data extraction and compared the validity of the data until consensus was reached.

Statistical analysis

The categorical outcomes were evaluated by means of the Odds Ratio (ORs) and the 95% confidence interval (95% CI) were calculated by means of Fixed-Effects or Random-Effects model (Mantel-Haenszel statistical method). OR<1 denoted outcome that was greater in the RT group. Continuous outcomes were calculated by means of weighted mean difference (WMD) with its 95% CI, using Fixed-Effects or Random-Effects (Inverse Variance statistical method) models, appropriately, in order to measure pooled estimates. In cases where WMD < 0, the variables in the RT group were increased. The Cochran Q statistic and the I^2 were calculated in order to assess the between-study heterogeneity.[9] Forest plots were produced regarding the variables that were analyzed.

Quality and publication bias evaluation

The Newcastle-Ottawa Quality Assessment Scale (NOS)[10] was used in order to assess all non-Randomized Controlled Trials (non-RCTs) that were included. The scale ranges from zero to nine stars. The studies that were evaluated with a score equal to or higher than five were considered to have a good level of methodological quality and were finally included. No RCTs were identified and included in the current meta-analysis. Two authors (AD, DEM) rated the included studies independently and a final decision was reached by consensus.

The risk of publication bias was evaluated by the visual inspection of funnel plots. Publication bias could not be further evaluated by means of the Egger's formal statistical test[11] due to the small number of the included studies (less than 10). As a result, the power of the test was significantly compromised.

Results

Article selection and patient baseline characteristics

The flow diagram of the present systematic review and meta-analysis is presented in Figure 1 *(Prisma Flowchart)* and the *Prisma Checklist*. In total, 374 ar-

TABLE 1. Characteristics

Study ID,Year	Journal	Country	Time Period	Type of Study	Patients, n		Female, n (%)		Median Age(Range)		Stars In Ottawa
					SA	RT+S	SA	RT+S	SA	RT+S	
Kelly et al., 2015 [12]	Ann Surg	USA	2003-2011	R	172	32[1]	84 (49%)	17 (53%)	62 (26-92)	57 (41-85)	6
Lane et al., 2015 [13]	J Surg Onc	USA	-	R	45	29	23 (51,1%)	16 (55,2%)	60 (52, 68)	57 (51, 61)	5
Nussbaum et al., 2016 [14]	Lancet Oncol	USA	2003-2011	R	3322	563[1], 2196[2]	1713 (51,5%)	250 (44%) 138 (52%)	59,5 (± 14,5)	59,2 (±13,8), 59,5 (±13,9)	6
Pierie et al., 2006 [15]	EJSO	USA	1973-1998	P	21	41[2]	N/A	N/A	N/A	N/A	5
Smith et al., 2014 [16]	Radiother Oncol	Canada	1996-2000	R	104	40[1]	49 (47%)	25 (62%)	N/A	N/A	6
Stoeckle et al., 2001 [7]	Cancer	France	1980-1994	R	55	89[2]	N/A	N/A	N/A	N/A	5
Stucky et al., 2014 [17]	J Surg Onc	USA	1996-2011	R	26	37[1]	9 (35%)	17 (46%)	74	56	6
Toulmonde et al., 2014 [18]	Annals of Oncology	France	1988-2008	R	262	127	-	-	-	-	5
Trovik et al., 2014 [19]	Acta Oncologica	Sweden	1988-2009	R	55	42	22 (58,2%)	15 (33%)	63(15-83)	61(35-82)	6
Zhou et al., 2010 [20]	Arch Surg	USA	1988-2005	R	1175	372[2]	-	-	-	-	5

SA = Surgery Alone; RT+S = radiotherapy+ Surgery); 1 = preoperative radiotherapy; 2 = postoperative radiotherapy

TABLE 2. Summary of the analysis of the categorical and continuous outcomes

Categorical Outcomes	n	OR (95% CI)*	p	Heterogeneity	
				I^2	p
5-year OS total	9	0.69 [0.62, 0.77]	<0.0001	67 %	0.002
5-year OS preoperative RT	5	0.69 [0.56, 0.85]	0.0005	50 %	0.09
5-year OS postoperative RT	4	0.69 [0.61, 0.79]	<0.0001	82 %	0.001
RFS total	6	0.33 [0.24, 0.46]	<0.0001	69 %	0.006
RFS preoperative RT	4	0.19 [0.11, 0.33]	<0.0001	72 %	0.001
RFS postoperative RT	2	0.49 [0.32, 0.75]	0.001	0 %	0.81
R0 resections total	3	0.90 [0.81, 0.99]	0.03	69 %	0.04
R0 resections preoperative RT	2	1.21 [0.65, 2.25]	0.56	82 %	0.02
R0 resections postoperative RT	1	0.89 [0.81, 0.98]	0.02	N/A	-
Continuous outcomes	n	WMD (95% CI)	p	I^2	p
MOS total	5	-18.94 [-19.14, -18.74]	<0.0001	100 %	< 0.0001
MOS preoperative RT	2	-22.93 [-27.91, -17.96]	<0.0001	30 %	0.23
MOS postoperative RT	3	-18.93 [-19.13, -18.74]	<0.0001	100 %	< 0.0001-

CI = Confidence Intervals; MOS = Median Overall Survival; OR = Odds Ratio; OS = Overall Survival; RFS = Recurrence Free Survival; RT = Radiotherapy; WMD=Weighted Mean Difference

ticles that were originally identified in PubMed, Scopus, and CENTRAL databases and ten articles were finally included in the quantitative synthesis.[7,12-20] The level of agreement between the two reviewers was "very good" (kappa = 0.730; 95% CI: 0.503, 0.957). The study design was retrospective in nine studies[7,12-14,16-20] and prospective in one study.[15] The total baseline characteristics of the included studies are shown in Table 1. The Newcastle-Ottawa Scale (NOS) regarding all included studies and the quality assessment of the RCTs is presented in Table 1. Pooled ORs, I^2 along with *p values*

of heterogeneity regarding all outcomes that were measured are summarized in Table 2.

Median overall survival (median-OS)

The median OS was significantly higher in patients treated with preoperative RT followed by surgery compared to surgery alone (WMD: -22.93 [95% CI: -27.91, -17.96]; *p* < 0.0001). The median-OS was also significantly higher in patients treated with surgical resection followed by postoperative RT compared to surgery alone group (WMD: -18.93 [95%

CI: -19.13, -18.74]; p < 0.0001). According to the total analysis, the median OS was significantly increased in patients treated with surgical resection and either neoadjuvant or adjuvant radiotherapy compared to surgery alone (WMD: -18.94 [95% CI: -19.14, -18.74]; p < 0.00001) (Figure 2).

5-year survival

The median 5-year survival was significantly increased in patients treated with preoperative RT followed by surgery compared to surgery alone (WMD: 0.69 [95% CI: 0.56, 0.85]; p = 0.005). The median 5-year survival was also significantly higher in patients treated with surgery followed by postoperative RT compared to surgery alone group (WMD: 0.69 [95% CI: 0.61, 0.79]; p < 0.0001). According to the total analysis, the 5-year survival was significantly increased in patients treated with surgery and either neoadjuvant or adjuvant therapy compared to surgery alone (WMD: 0.69 [95% CI: 0.62, 0.77]; p < 0.0001) (Figure 3).

Median recurrence-free survival

The median RFS was significantly increased in patients treated with surgical resection and either preoperative (WMD: 0.19 [95% CI: 0.11, 0.33]; p < 0.0001) or postoperative (WMD: 0.49 [95% CI: 0.32, 0.75]; p = 0.001) RT compared to surgery alone (Figure 4).

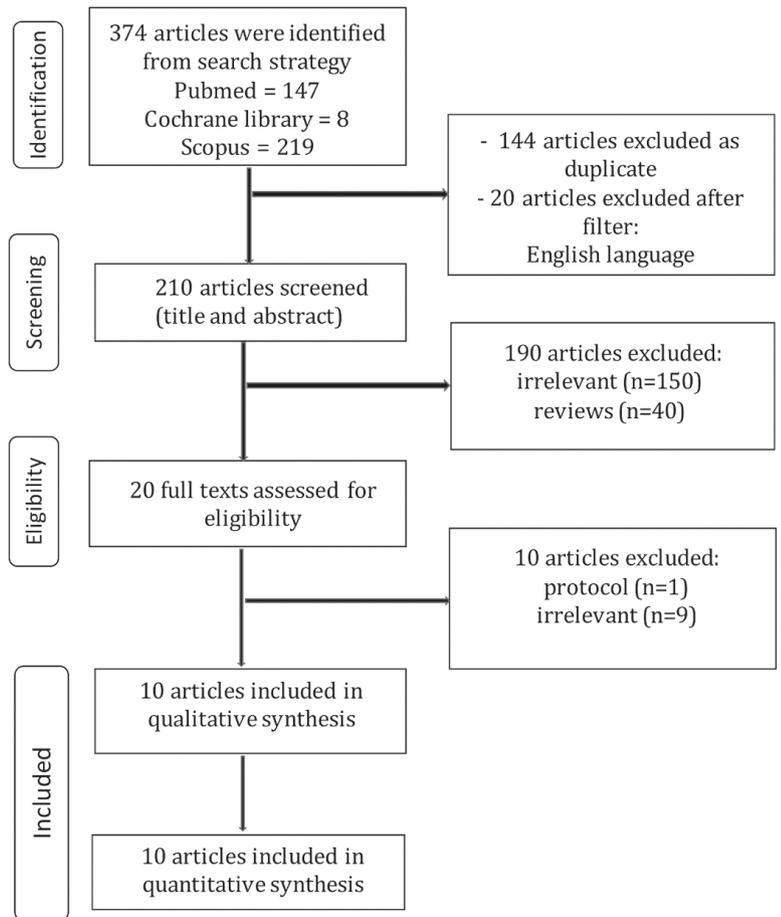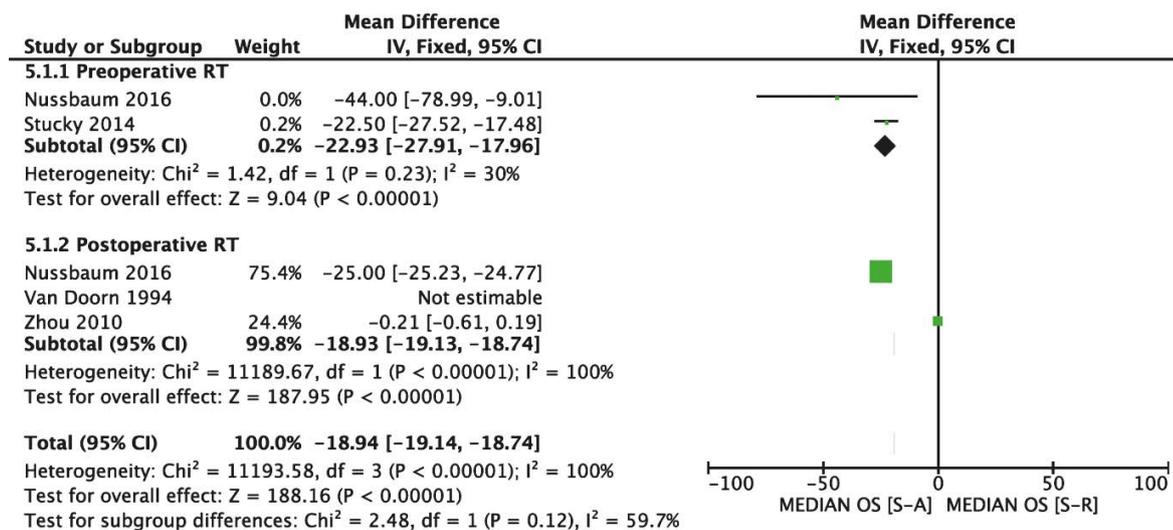**FIGURE 1.** Prisma flowchart.

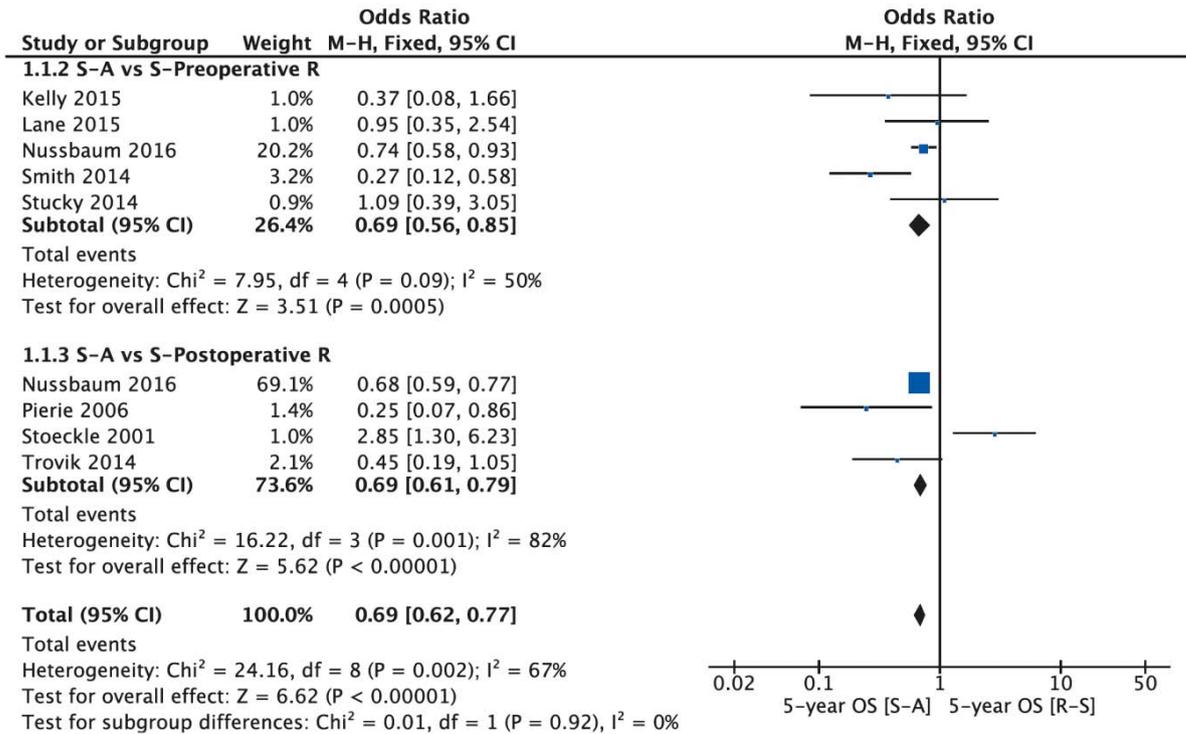

FIGURE 2. Median overall survival.
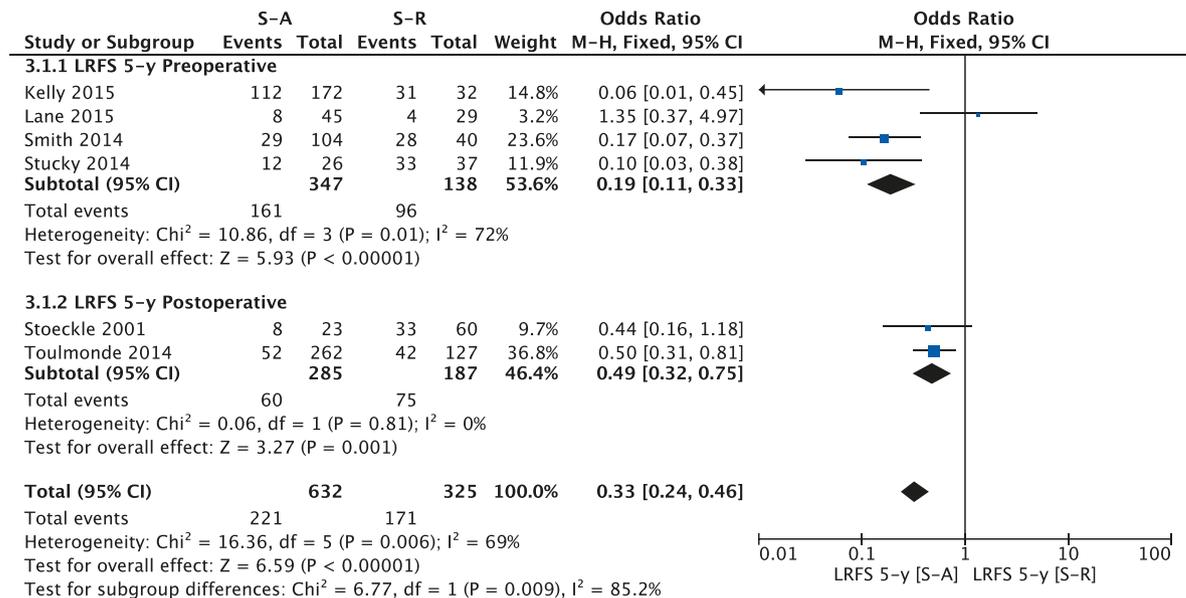
FIGURE 3. 5-year overall survival.

FIGURE 4. Median recurrence-free survival

R0 resection rate

The median R0 resection rate was similar between the groups of neoadjuvant therapy plus surgery compared to surgery alone (WMD: 1.21 [95% CI: 0.65, 2.25]; p = 0.56) (Figure 5).

Publication bias

Funnel plots seemed asymmetrical, with studies being absent from either top or bottom of the graph, thus posing certain publication bias. The small number of included studies was the main
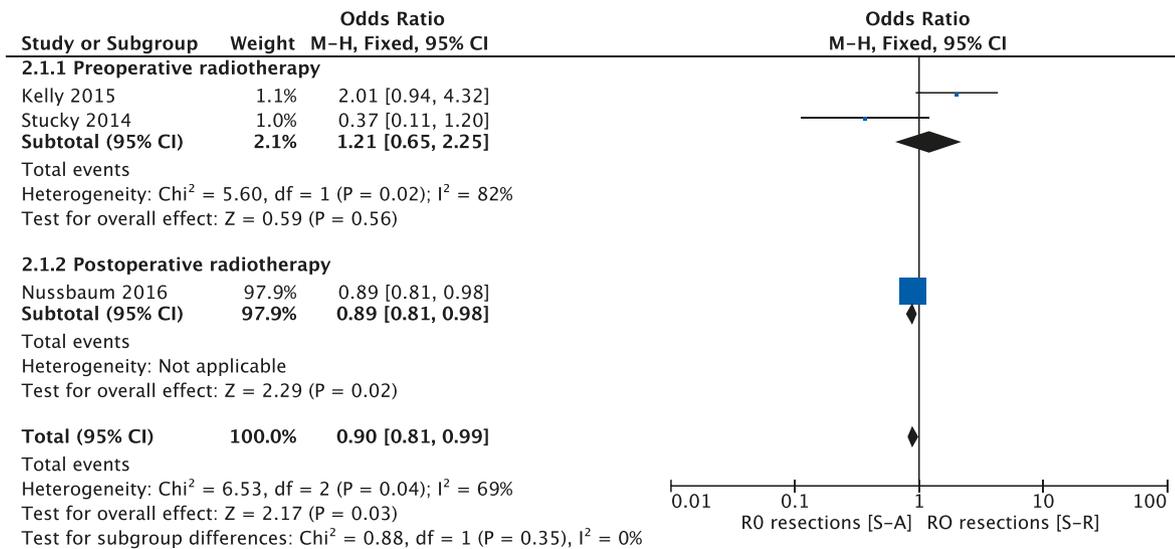
FIGURE 5. R0 resection rate.

reason for the reported asymmetry. Egger test could not be performed because of the inadequate number of studies that were included. Finally, data retrieved is all but in one from retrospective studies and no randomized studies were included.

Discussion

Notwithstanding all the accumulated experience and knowledge regarding the diagnosis and treatment of patients with RPS through the past years, still, those patients' management remains challenging. Current literature evidence is quite insufficient on treatment strategies based mainly on retrospective single-center series, covering small patients' numbers, and treated with various combinations of surgical approaches, with or without adjuvant treatment modalities.

Surgical resection is adequate only when R0 excision of the RPS is feasible. However, due to its late presentation and its tendency to grow in close proximity with vital abdominal structures, in many cases, multivisceral excisions are needed to achieve a good oncologic outcome making it quite difficult to avoid either macroscopic or microscopic residual disease. RPS is often diagnosed in advanced stage, as it is often asymptomatic, and it makes complete excision difficult. Even after aggressive surgical treatment, the median survival of affected patients is 74 months and 5-year all survival rate is 36-58% with recurrence rates often >50%[1,2,4], dictating the need of better local control of the disease.

On this basis, RT could be a logical addition to the patient's management. Only a few studies have tested in a prospective manner the efficacy of RT in patients with RPS either on a neoadjuvant or adjuvant setting. Pierie *et al.*, studied prospectively 103 consecutive patients who were treated for primary RPS and concluded that the most important factor influencing OS and recurrence rate was the complete resection of the disease, and only in patients at high risk of recurrence (*i.e.* high-grade tumors, positive microscopic margins) the addition of RT (IORT plus EBRT) can improve OS and local control of the disease with acceptable level of complications.[15]

Stucky *et al.*, after reviewing 63 consecutive RPS patients concluded that the combination of preoperative radiation plus surgical resection and intraoperative radiation results in excellent local disease control for RPS but not respectively improves overall survival.[17] Moreover, postoperative RT improves the local control of the disease in combination with conservative surgery in patients with negative, marginal or minimally microscopically positive surgical margins. Stoeckle *et al.* stated that adjuvant RT represents the most important prognostic factor for local control of the disease since it is associated with significantly reduced local recurrence rates.[7] High-grade tumors and margin positivity status are at higher risk for local failure and can be considered for intensification of therapy.[15] The combination of surgery, Intraoperative RT (IORT) plus External Beam RT (EBRT) yields favorable local control and survival data.[27] On the

contrary, Pirayeshand *et al.*, re-emphasized the poor outcome of patients with RPS and failed to find any connection between adjuvant RT or chemotherapy and a better outcome either on survival or local control of the disease.[21]

In our metanalysis, it was found that RT delivered either preoperatively or postoperatively, is associated with better median overall and median 5-year survival. In concordance with the results of other retrospective studies, perioperative RT also favors recurrence-free survival compared to surgery alone.[12,13,16] Interestingly, RT did not affect the R0 resection rates as previously reported in the literature.[12] Thus, patients with RPS should be assessed within a multidisciplinary sarcoma tumor board in order to consider RT in their treatment strategy.

Regardless of the timing chosen for RT, physicians should also try to limit the dose of radiation to the surrounding normal tissues. High attention is required in regards to the small bowel, especially in the setting of adjuvant treatment, that may fall into space previously occupied by the removed sarcoma mass and get exposed to high doses of irradiation resulting sometimes in serious complications even in perforation and peritonitis if incidental inclusion of the bowel occurs, especially during IORT.[24] According to current experience, preoperative radiotherapy should be probably preferred. More specifically, the potential advantages of preoperative RT treatment are a) The decrease of residual microscopic local malignant cells. b) Radiosensitivity is higher due to better-oxygenated cells since postsurgical area represents a potentially more radio-resistant hypoxic region). A more radiosensitive target allows the delivery of lower doses of radiation, smaller field sizes and lower toxic adverse events from surrounding organs at risk.[23-25] c) Postoperative adhesions can induce inhomogeneities in the radiotherapeutic treatment plan and suboptimal RT delivery. d) RT can lead to tumor down-sizing / staging. e) RT enables more limited surgery and reduces the amount of normal tissue that needs to be removed. f) RT decreases tumor seeding at the time of surgery. g) In some cases of marginally resectable locally advanced disease, RT can achieve resectability. h) RT may increase R0 resection rate as a result of pseudocapsule that forms around the tumor.[26]

In the modern era, the use of newer and more sophisticated RT techniques as 3D-CRT and IMRT and conformal treatment planning can facilitate surrounding normal organ sparing and avoid acute radiation-adverse events such as enteritis,

anorexia, nausea/vomiting and late sequelae as peritonitis.[28] CT simulation and four-dimensional CT (4D-CT) scan for the assessment of the respiratory movement, allow the minimization of the RT dose to the normal tissues, and reduce the incidence of toxicity with excellent local control of the disease.[28-30]

Given the rarity of the disease, proper treatment of RPS must be investigated and determined only after multi-institutional participation in large randomized control trials. STRASS trial is the first, phase III, randomized, multicenter, EORTC study trying to assess whether there is a difference in abdominal recurrence-free survival between RPS patients treated with preoperative RT followed by surgery compared to surgery alone.[22] The results of STRASS trial were presented at the ASCO meeting in 2019 and failed to demonstrate a benefit of preoperative RT for RPS showing no difference in RFS between neoadjuvant RT and surgery vs. surgery alone arms with the exception of liposarcomas in an unplanned subset analysis. There was also, no difference in OS between the two groups. However, in the propensity matched analysis, there was a trend towards improved RFS and LR in the RT arm.

Limitations

Several limitations should be considered before appraising the results of this study. The limitations of this meta-analysis reflect the limitations of the studies included. Nine studies (90%) were retrospective[7,12,13,15-20] and one study (10%) was prospective.[14] No RCT was included. The studies used in this meta-analysis exhibit considerable heterogeneity, limiting the validity of the comparisons between studies and conclusions drawn. Finally, the small number of the included studies poses a publication bias, as it reflects the asymmetry of funnel plots.

Conclusions

After taking into consideration certain limitations, in our metanalysis perioperative RT is associated with improved OS and lower recurrence rates and should be offered selectively, to patients with RPS in the frame of a multidisciplinary team meeting. However, multicentered randomized trials are needed to confirm or revoke these results and assess which patients with RPS could have the greatest clinical and oncological benefit. If the results of these trials confirm the results of our meta-anal-

ysis, which until now comprise the best evidence available, RT along with radical surgery could be the standard of care in at least a subgroup of patients with RPS. This subgroup taking into consideration the STRASS trial's results is probably the LPS subgroup, but this remains to be confirmed in future studies.

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