Definitive radiotherapy in the management of non-resectable or residual retroperitoneal sarcomas: institutional cohort analysis and systematic review

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Research

Keywords: Sarcoma; Radiotherapy; Retroperitoneal Neoplasms; Radiotherapy, Intensity-Modulated; Radiotherapy, Image-Guided; Abdominal Neoplasms

DOI: https://doi.org/10.21203/rs.3.rs-30463/v1

Abstract

Background There is currently no consensus on optimal management of patients with primary or recurrent non-resectable/residual retroperitoneal sarcomas (RPS). The objective of this study was to document the outcomes of patients with primary or recurrent non-resectable/residual RPS treated in our center with definitive radiotherapy (RT), and to perform systematic review on that topic.

Methods A retrospective analysis of consecutive RPS patients treated in our center between 2000 and 2019 was performed. All consecutive patients who underwent definitive conformal RT with image guidance for primary or recurrent non-resectable or macroscopically residual RPS were included. Additionally, the systematic review compliant with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was performed.

Results 14 patients who met aforementioned criteria were found. Data on clinicopathological characteristics, RT and response to treatment were presented. RT allowed achieving prolonged local control of the disease i.e. no local progression of the disease for more than six months after RT in 12 patients. Achieved local control lasted more than 24 months in six cases, with none or minimal toxicity. 11 studies were included in the systematic review. Our results are in concordance to reports included in the review.

Conclusions RT provided satisfactory local disease control with acceptable treatment tolerance in patients with primary or recurrent non-resectable/residual RPS. RT represents valuable treatment modality in this selected group of patients. Additional RT modalities i.e. particle therapy, MRI-guided RT or GRID/Lattice RT may be introduced to improve local control and minimize toxicity.

Background

Retroperitoneal sarcomas (RPS) – accounting for 15% of all soft tissue sarcomas (STS), are rare neoplasms with general incidence rate in Europe of 0.31 per 100,000 people per year [1]. Due to their localization, which constrict surgical access and enable asymptomatic RPS growth until large size and vital organs involvement, management of RPS is challenging and has often unsatisfactory results [2]. In epidemiologic data retrospective analysis from 45 European cancer registries 5-year relative survival rate of patients with RPS between 1995 and 2007 reached only 38.8% (95% confidence interval 37.1–40.5) [1]. In more recent analysis of 1007 patients treated at the two North American and six European sarcoma centers, after median follow-up of 58 months, 5, 8, and 10-year overall survival were 67%, 56% and 46%, respectively [3]. Surgery is the primary treatment modality for RPS and microscopically radical (R0) resection is correlated with decreased rate of abdominal recurrence and significantly longer survival [4–6]. However, patients with gross residual disease after surgery (R2) seem to have no survival benefit from surgery when compared to patients classified as non-resectable [5]. Moreover, even when performed resection was optimal, the 5-year local control rate remains low, between 27% and 62% depending on the report [7]. The most common cause for RPS treatment failure is local recurrence; in an aforementioned analysis of 1007 patients treated surgically for primary RPS, 316 of them developed local recurrence and in 249 cases it was the first sign of disease progression [3]. Locally advanced, recurrent or non-resectable RPS prompted administration of neoadjuvant and adjuvant therapies, namely radiotherapy (RT) and chemotherapy; however, their role in management of primary RPS remains uncertain [8,9]. The use of RT in RPS is limited due to the predictable large target volumes and significant volume of adjacent radiosensitive organs at risk (OARs), such as small bowel. Recently, STRASS trial, a phase III randomized study of preoperative RT with surgery versus surgery alone for patients with primary RPS, failed to demonstrate a benefit of neoadjuvant RT in RPS management in the entire study population, and local control was improved in analysis of liposarcoma subgroup only [10]. Thus, there is no strong evidence to support perioperative RT as a routine practice in primary resectable RPS [11]. In case of locally recurrent resectable RPS, National Comprehensive Cancer Network recommendations suggest secondary surgery with or without intraoperative RT or neoadjuvant radio(chemo)therapy. Similarly, the European Society for Medical Oncology guidelines recommend individualized approach with surgery, especially in patients with long disease-free period [12]. In the consensus-based guidelines from the Trans-Atlantic Retroperitoneal Sarcoma Working Group secondary surgery with or without RT is also presented as treatment of choice, however it is underlined that the risk of morbidity may be substantial, thus patient should be selected very carefully [13]. There is currently no consensus on optimal management of patients with primary or recurrent non-resectable/residual RPS. Contemporary conformal RT techniques with image guidance (IGRT) could be valuable, but underestimated modalities in this group of patients. The purpose of this analysis was to document the outcomes of patients with primary or recurrent non-resectable/residual RPS treated in our center with definitive IGRT. We also conducted a systematic review of the literature concerning this issue, to analyze the outcomes and safety profile of management of primary or recurrent non-resectable/residual RPS with RT.

Methods

Analyzed group

A retrospective analysis of consecutive nonmetastatic RPS patients treated in our center between 2000 and 2019 was performed. We included all consecutive patients who underwent definitive IGRT for primary or recurrent non-resectable or macroscopically residual RPS. Treatment mode including surgery and RT were assessed by the sarcoma multidisciplinary tumor board including surgical oncologists, radiation oncologists, medical oncologists and radiologists. Treatment of primary RPS was typical with surgery with or without chemotherapy (most often doxorubicin-based regimen) [14]. Pathological diagnoses were compliant with WHO Classification of Tumours of Soft Tissue and Bone 4th Edition [15]. All pathological diagnoses were centrally reviewed in our center by experienced sarcoma pathologist.

Radiotherapy

IGRT was defined as RT techniques planned in three dimensions with image guidance (planar kilovoltage or cone beam computed tomography), namely three-dimensional conformal RT (3D-RT), intensity-modulated RT (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic body RT (SBRT). SBRT was defined as delivery of dose higher than 4 Gy per fraction, prescribed to gross tumor volume without elective margin. The following parameters included in the

analysis: pathology of primary tumor, indication for RT, previous or concomitant systemic therapy, RT technique, total dose, equivalent 2-Gy dose (EQD2), dose per fraction, target volumes, early and late RT toxicity, best local response, incidence of local or distant relapse, date of disease progression, date of death (if applicable). Literature data suggests various, but often low alpha/beta ratio of sarcomas, mostly between 0.4 and 5 Gy [16]. Thus, we assumed alpha/beta ratio of sarcomas as 3 to calculate EQD2 [17].

Data extraction

Electronic medical records were screened with MedStream Designer software (Transition Technologies). Corresponding International Classification of Diseases code C48, C49, and keyword “radiotherapy” were used. All data was reviewed independently by two researchers.

Statistical analysis

Descriptive statistics: as measures of frequency: count, percent, frequency were used; as measures of central tendency - mean and median and as measures of dispersion or variation range, variance and standard deviation [18]. Toxicity was reassessed according to Common Terminology Criteria for Adverse Events 5.0. Best local response was assessed using Response Evaluation Criteria In Solid Tumors 1.1 (RECIST). Prolonged local control was defined as no local disease progression at least for six months after IGRT. It was calculated as a difference in months between the RT and date of disease local progression (if occurred) or last follow-up. Missing data regarding the date of death were obtained from the National Cancer Registry. In case of death from unknown reasons, the patient was treated as dead of disease progression.

Systematic Review

The review was conducted according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19]. Online databases: PubMed, Scopus and Embase were searched using the following formula of keywords: retroperitoneal AND sarcoma AND radiotherapy AND (non-resectable OR unresectable OR inoperable OR residual). Only full-text publications in English were included. There were no limits on the date of publication. Included papers were original reports concerning definitive RT of primary or recurrent non-resectable or macroscopically residual RPS. Review articles and. publications assessing RT as a neo- or adjuvant treatment to surgery or only with palliative intent were excluded. The search of databases was supplemented with the “related articles” function, hand searches of reference lists of all available review articles, meta-analyses, original studies and handbooks. Review of the articles was performed by two authors independently, and any publications which were differentially classified were once again thoroughly evaluated based on inclusion criteria. Data concerning clinical characteristics of enrolled patients, RT techniques, total dose, dose per fraction, early and late RT toxicity, local control rates and survival outcomes was then extracted by one author with the accuracy checked by the second author.

Results

Between 2000 and 2019 14 patients were treated for non-resectable/residual RPS with definitive IGRT in our center. Data on clinicopathological characteristics, RT and response to treatment were summarized in Table 1.

Table 1. Case series of patients with primary or recurrent non-resectable/residual RPS treated in our center with definitive IGRT

Pt #	Sex	Age at RT (y)	Pathologic diagnosis	Indication for RT	Previous treatment	RT technique	RT year	Total dose (Gy)	Dose per fraction (Gy)	EQD2 (Gy)	PTV (cm^3)	Best response, RECIST	Follow-up time (months)	Length of local response[&] (months)	Prolonged local response[&]	Local PD[&]	D P
1	F	58	UPS G3	residual	R+CHT (ADIC)	IMRT/VMAT	2009	64.0	2.0	64.0	635	PR	29.0	23.8	Yes	Yes	N
2	M	57	LMS G2	primary NR	CHT (ADIC)	3D-RT	2011	46.0	2.0	46.0	NA	PR	29.1	27.7	Yes	Yes	N
3	M	57	LMS G2	recurrent NR	R	3D-RT	2012	57.6	1.8	55.3	1076	PR	44.4	24.7	Yes	Yes	N
4	M	30	undifferentiated sarcoma NOS G2	primary NR	None	IMRT/VMAT	2014	50.0	2.0	50.0	781	PD	3.6	NA*	No	Yes	N
5	F	43	MPNST G1	residual	R	IMRT/VMAT	2014	66.0	2.0	66.0	69	SD	14.2	14.2	Yes	No	N
6	M	58	LMS G2	recurrent NR	R+CHT (ADIC)	IMRT/VMAT	2014	66.0	2.0	66.0	1033	PR	36.8	36.8	Yes	No	Y
7	M	26	LMS G2	recurrent NR	R+CHT (ADIC)	IMRT/VMAT	2015	66.0	2.0	66.0	41	SD	3.0	3.0	No	No	N
8	F	44	MPNST G1	primary NR	None	IMRT/VMAT	2015	66.0	2.0	66.0	1462	SD	11.7	11.7	Yes	No	Y
9	M	29	synovial sarcoma	recurrent NR	R+CHT (AI; EI; GD; CyADIC)	IMRT/VMAT	2015	66.0	2.0	66.0	1028	SD	59.0	59.0	Yes	No	Y
10	F	58	MPNST G3	residual	R	IMRT/VMAT	2015	66.0	2.0	66.0	670	PR	56.4	56.4	Yes	No	N
11	F	63	myxoid LMS G2	primary NR	CHT (ADIC+DDP; GC+DTIC; trabectedin)	IMRT/VMAT + deep hyperthermia	2019	39.0	3.0	46.8	774	SD	6.5	6.5	Yes	No	Y
12	M	68	dedifferentiated LPS G2	recurrent NR	R	SBRT	2019	50.0	5.0	80.0	154	SD	8.5	8.5	Yes	No	N
13	F	62	LMS G3	recurrent NR	R+CHT (CyADIC)	IMRT/VMAT SIB	2019	30.0 /45.0	3.0 /4.5	54.0	305	PR	12.4	12.4	Yes	No	N
14	M	71	well-differentiated LPS G1	recurrent NR	R+CHT (ADIC)	SBRT	2019	30.0	6.0	54.0	27	SD	9.8	19.8	Yes	No	N

Abbreviations: 3D-RT - three-dimensional conformal radiotherapy; A – alive; ADIC – dacarbazine; doxorubicin; AI – doxorubicin, ifosfamide; AWD – alive with disease; cyADIC – cyclophosphamide, dacarbazine, doxorubicin; DDP – cisplatin; DOD – death of other disease; DP – death of disease progression; DTIC – dacarbazine; EI – epirubicin, ifosfamide; F – female; G – grade; GC – gemcitabine; GD – gemcitabine, docetaxel; IGRT – image-guided radiotherapy; IMRT – intensity modulated radiotherapy; LMS - leiomyosarcoma; LPS – liposarcoma; LTFU – lost to follow-up; M – male; MPNST – malignant peripheral nerve sheath tumour; NA - not applicable; ND – no data; NR - non-resectable; PD – progressive disease; Pt. – patient(s); PR – partial response; PTV – planned target volume; R - resection; SBRT – stereotactic body radiotherapy; SD – stable disease; SIB – simultaneous integrated boost; UPS – undifferentiated pleomorphic sarcoma; VMAT – volumetric modulated arc therapy; y – year(s)

* - local progression in the first imaging after RT
# - missing data were obtained from the National Cancer Registry
& - in case of lost to follow-up or death, it was calculated and presented until the last available follow-up

Eight of 14 patients were male, median age reached 58 years (range: 29–71). The most common pathologic diagnosis was leiomyosarcoma, which accounted for 42.8% of cases. Seven of 14 patients were treated for recurrent non-resectable disease, four for primary non-resectable disease and three for residual disease. Among the patients who had received previous treatment, majority had been treated with surgery and chemotherapy (most often dacarbazine and doxorubicin regimen). RT technique was IMRT/VMAT in ten out of 14 patients; while SBRT and 3D-RT were applied in two cases each. Median total dose reached 60.8 Gy (range: 30.0-66.0 Gy), median dose per fraction was 2.0 Gy (range: 1.8–5.0 Gy) and median EQD2 was 65.0 Gy (range: 46.0-80.0 Gy). Median gross tumor, clinical target and planned target volumes were as follows: 142.5 cm^3 (range: 9.0-550.0 cm^3), 515.0 cm^3 (range: 27.0-1144.0 cm^3), and 652.5 cm^3 (range: 41.0–1462.0 cm^3). Best response to treatment according to RECIST was partial response, and it was achieved in six patients, while seven patients had stable disease, and one patient progressed despite RT. Thus, clinical benefit was seen in 13 of 14 patients (93%). Prolonged local control (i.e. at least for six months) was observed in 12 patients (86%). There were four events of early toxicity observed in three patients (two grade 1 gastrointestinal toxicities, one grade 1 skin toxicity and one case of mild pain within the irradiated volume). Late toxicities occurred in two patients and manifested as grade 1 skin toxicity and persistent mild pain within the irradiated volume.

Figure 1 shows the PRISMA flow diagram, documenting the number of search results, publications excluded after title/abstract review and full-text review and the number of articles meeting the inclusion criteria. A total of 11 studies were included in this review, and the extracted data was summarized in the Table 2 and Table 3 [20–30].

Table 2. Systematic review of literature concerning patients with primary or recurrent non-resectable/residual RPS treated with definitive RT: case reports

First author (year)	Sex	Age at RT (y)	Pathologic diagnosis	Indication for RT	RT technique	Total dose	Dose per fraction	Best response, RECIST	Length of local response (months)	PD	Early toxicity	Late toxicity	Recent status
Kumar (1986)	M	43	MPNST	recurrent NR	BT	160 Gy	14.8 MBq per seed	SD	24	No	ND	ND	NED
Shelat (2009)	M	64	LPS	primary NR	photon RT	ND	ND	PR	6	No	chylous ascites	none occurred	AWD
Akhavan (2012)	F	57	MPNST	residual	2D	60 Gy	1.8 Gy	CR	4	No	none occurred	none occurred	NED
Li (2013)	F	60	LMS	primary NR	BT	2x 30 ^{125}I seeds	0.8 mCi per seed	CR	33	No	none occurred	inferior vena cava thrombosis	NED
Sagara (2014)	F	65	pleomorphic LMS	residual	photon RT	50 Gy	2 Gy	SD	17	No	none occurred	none occurred	AWD
Brenneman (2019)	F	67	unclassified round cell sarcoma	primary NR + metastases	proton RT	50 CGE	2 CGE	CR	18	No	G1 lymphopenia	none occurred	NED
Xu-Holland (2019)	F	ND	LMS	primary NR	VMAT	60 Gy	2 Gy	PR	ND	ND	no acute toxicity over G1	ND	AWD

Abbreviations: 2D – two dimensional radiotherapy; AWD – alive with disease; BT – brachytherapy; CGE - Cobalt Gray Equivalents; CR – complete response; F – female; G – grade; LMS - leiomyosarcoma; LPS – liposarcoma; M – male; MPNST – malignant peripheral nerve sheath tumour; ND – no data; NED – no evidence of disease; NR - non-resectable; PD – progressive disease; PR – partial response; VMAT – volumetric modulated arc therapy; y - year(s)

Table 3. Systematic review of literature concerning patients with primary or recurrent non-resectable/residual RPS treated with definitive RT: institutional case series and retrospective analyses

First author (year)	No. of Pts @ Sex	Age at RT (y)	Pathologic diagnosis	Indication for RT	RT tech.	Total dose	Dose per fraction	LCR	Early tox.	Late tox.	OS
Serizawa (2009)	24 @ 17M, 7F	median 48.6 (16-77)	6 UPS; 3 LPS; 3 MPNST; 2 Ewing sarcoma; 10 other	16 primary NR 8 recurrent NR	CIRT	median 70.4 GyE (52.8-73.6)	3.3 GyE - 4.6 GyE	2y: 77% 5y: 69% 6 of 24 had local progression during mean 41m of FU	20 G1 & 4 G2 skin tox.; 1 G1 pulmonary tox.	22 G1 & 1 G2 skin tox.; 5 G2 neurologic tox.	2y: 75% 5y: 50%
Greiner (1992)	21 @ ND on sex	median 53 (8-69)	7 LPS; 4 LMS; 2 MPNST; 6 other	10 primary NR 4 recurrent NR 7 residual	pion RT	median 32.3 Gy (30-34.6)	1.5 Gy - 1.8 Gy	3y: 90% 5y: 60% 3 out of 21 had local PD after 3, 8 and 41m after RT	majority of pt. had G1 upper GI tox.	1 hepatic tox.; 1 G4 skin tox.; 1 lower extremity edema; 2 GI obstructions (RT was not the immediate cause)	3y: 67% 5y: 33%
Feng (2007)	85 (68 with RPS) @ 45 M, 43 F	median 52 (19-79)	31 LMS; 20 LPS; 15 UPS; 8 MPNST; 14 other	13 NR 12 residual 63 RT was adjuvant to resection	3D-RT	median 56.4 Gy	ND	LCR only included patients with adjuvant RT DFS included the entire cohort: 1y: 75%, 2y: 53%, 5y: 30%	3 G3 vomiting; 1 G3 diarrhea	3 G3 GI obstruction; 1 G3 GI bleeding; 1 G3 abdominal wall fibrosis; 1 G3 cystitis; 1 G3 wound healing difficulty	2y: 70% 5y: 34%
Yang (2016)	23 @ 9M, 14F	median 50.17 (19-78)	6 LPS; 6 LMS; 2 round cell LPS; 3 epithelioid sarcoma; 2 RMS; 4 other	2 primary NR 11 recurrent NR	BT	mean 70.87 (10-210) ^{125}I seeds	0.78 mCi per seed	87% after 20.8±13.2m of FU	Time of events was not reported 4 fever; 3 seed drafts; 4 G1 upper GI tox.; 3 G1 lower GI tox; 1 intestinal bleeding; 1 stent-tract bleeding		median 21.56±14.16m

Abbreviations: 3D-RT – three-dimensional conformal radiotherapy; BT – brachytherapy; CIRT – carbon-ion radiotherapy; DFS – disease free survival; F – female; FU – follow-up; G – grade; GI – gastrointestinal; LCR – local control rate; LMS – leiomyosarcoma; LPS – liposarcoma; m – month(s); M – male; MPNST – malignant, peripheral nerve sheath tumor; ND – no data; NED – no evidence of disease; NR – non-resectable; OS – overall survival; PD – progressive disease; pt. – patient(s); RMS – rhabdomyosarcoma; RT – radiotherapy; tox. – toxicity; UPS – undifferentiated pleomorphic sarcoma; y – year(s)

Discussion

In our report, contemporary IGRT allowed achieving prolonged local control of the disease in 86% of patients. Moreover, achieved local control lasted more than 24 months in six cases (43%), indicating vast clinical benefit from RT. At the same time, good treatment tolerance was sustained with minimal acute toxicity – grade 1 acute toxicity developed only in four patients and higher-grade toxicities were not observed. This is in concordance to reports included in our systemic review – in majority of described cases no acute toxicities were reported, and if so, then those toxicities were mild and assessed as grade 1. In the reviewed articles, acute toxicity most commonly involved skin and gastrointestinal tract. Late toxicities, which in our report occurred only in two patients, were also mild and manageable. In the reviewed articles, late toxicities were rare and typically involved skin and nervous system. They were mild in most cases, however there was one grade 4 skin toxicity reported by Greiner *et al.* (1992) [21] and several grade 3 toxicities reported by Feng *et al.* (2009) [23]. Surprisingly,

the most common pathologic types in our analysis were leiomyosarcoma and malignant peripheral nerve sheath tumor, while liposarcomas were rare - in reviewed reports liposarcomas accounted for the majority of cases or represented second most common subtype.

Data concerning definitive treatment of non-resectable/residual RPS with photon-based RT remains greatly limited, as it was applied in only five of the eleven reviewed reports. Recently, there was a short report published with a case report of two female patients with RPS treated with VMAT, however one of them was treated postoperatively, thus was not included in the Table 2 [30]. Delivery of a dose of 60 Gy was possible in both patients with satisfactory PTV coverage and keeping OARs within departmental dose constraints. In concordance to our results, no acute toxicity over grade 1 was observed. The report did not assess long term local control of the disease, apart from describing a minor response observed in a computed tomography scan performed post-treatment in the patient treated with definitive RT.

Optimal RT fractionation regimen in RPS has not been established. In a large retrospective analysis on patients with STS of different anatomic localizations treated with postoperative RT, it was shown that doses of 64 Gy or above are associated with significantly improved rates of local control in comparison to doses on the order of 60 Gy [31]. Delivery of such doses is substantially limited by frequent large volume of RPS and proximity of OARs. However, recent development of dynamic RT techniques resulted in the ability to shape the high dose region to precisely match complex target volumes, and greatly diminish the involvement of OARs [32]. This allowed for delivery of a EQD2 higher or equal to 64 Gy in half of the patients included in our report. SBRT, with doses per fraction greater than 4 Gy, was possible in only two patients whose GTVs were relatively small and allowed for precise RT planning with acceptable sparing of OARs. Regardless high EQD2 in one of applied fractionation regimens (50 Gy in 5 fractions, EQD2 80 Gy), no toxicities were observed. Development of MRI-guided RT allows for more detailed imaging of RPS to accurately distinguish their borders from OARs during RT planning, including SBRT [32]. In a case report by Ghanem *et al.* (2018) combination of MRI-guided RT with real-time MRI imaging enabled SBRT in management of a small cell lung cancer metastasis to retroperitoneal space in close contact with small bowel, achieving delivery of a dose of 27 Gy to the gross tumor volume in 3 fractions and durable near complete response, while preventing any acute gastrointestinal toxicity [33].

Advances in imaging techniques in RT resulted in adaptive radiation – correction of the RT plan on an ongoing basis as tumor volume changes during the treatment, which in STS applies to up to 60% of cases [34]. Either increase or decrease in size might be observed, as in a study by Haas *et al.* (2019) on extremity STS, changes in size during preoperative RT occurred in 58 out of 99 cases and in 41 of them increase was noted, while RT plan had to be adapted in eight cases [35]. Frequently observed temporary increase in size of STS during RT challenges the applicability of the dimension-based assessment of the response to the treatment according to RECIST criteria. European Organization for Research and Treatment of Cancer – Soft Tissue and Bone Sarcoma Group and Imaging Group recommend adoption of MRI techniques such as diffusion-weighted imaging to assist assessment of the STS response to RT, as diminished enhancement and rising apparent diffusion coefficient, resulting from development of necrosis, fibrosis and hyalinization of the tumor tissue indicate histopathological response [36].

Advanced RT delivery and planning techniques resulted in development of several approaches to the treatment of bulky tumors, such as spatially fractionated radiation therapy applied through sieve-like collimators, a so-called GRID therapy [37]. GRID further evolved into 3-D Lattice RT technique that restricts the high-dose regions to tumor volume [38]. They allowed for delivery of doses in range of 20 Gy to the tumor volume, with acceptable toxicities, due to grid-like pattern of affected and non-affected tissue resulting in faster rate of regeneration [38]. Lattice RT was shown in several case reports to enable durable local control with tolerable side-effects in management of large abdominal metastatic masses of gynecological neoplasms [39,40]. GRID combined with ifosfamide showed potential efficacy in the treatment of extremity STS, suggesting that those techniques may prove useful in management of large RPS [41].

Another RT technique potentially useful in RPS management may be brachytherapy (BT), which was applied in three papers included in our systematic review. In a series of 23 patients with non-resectable RPS treated with CT-guided ^{125}I implantation as the only treatment modality, BT seemed safe and efficient, causing mild side effects easily manageable with symptomatic treatment [22]. Significant decrease of visual analog scale score and objective response was achieved in all treated patients, with three local recurrences during mean 20.87 months of follow up. Additional to this analysis, there were two case reports concerning BT in RPS published, in which long lasting complete responses were achieved [24,27].

Recent decades brought development of RT techniques using charged particles, like protons and heavy ions, which due to Bragg curve can provide better dose distribution. Moreover, charged particles, such as carbon ions, deposit the radiation dose in a way that causes complex DNA damage at multiple sites, which are challenging for a single DNA damage response pathway to repair, making their usage in RT potentially effective in management of radio- and chemo-resistant tumors like STS [42,43]. The dose of particle-based RT is expressed in Gray-equivalents (GyE), calculated as carbon physical dose in Gy multiplied by Relative Biological Effectiveness (RBE), which in the case of carbon ions was empirically determined to equal 2.5 to 3, while protons are regarded as having RBE of 1.1. In a case series by Yoon et al. (2010) preoperative proton-beam radiation therapy in RPS was shown to allow marked sparing of OARs in comparison to IMRT [44]. In a prospective, phase 1 clinical trial of preoperative intensity modulated proton therapy for RPS, a dose escalation to 63 GyE was achieved with only mild acute toxicities and one late grade-3 hydronephrosis [45]. However, results of a parallel phase 1 study of the IMRT have not yet been published. Two papers included in our systematic review described efficacy of particle RT in the setting of unresectable RPS [20,29]. A case report by Brenneman *et al.* (2019) described a patient with metastatic RPS treated with proton beam RT, resulting in near complete response of the primary lesion and complete regression of all metastases [29]. Serizawa *et al.* (2009) published a case series of 24 patients treated with carbon ion RT (CIRT) for non-resectable RPS [20]. CIRT allowed for relatively high local disease control and satisfactory survival outcomes, with manageable toxicities, as most patients developed only grade $\leq$ 2 skin acute reactions. In a retrospective analysis by Imai *et al.* (2018), CIRT was shown to allow high irradiation doses with mild toxicity and satisfactory local control in non-resectable axial STS [46]. CIRT may also prove useful in the management of recurrent sarcomas in anatomical localizations hindering surgical access which can result in functional or aesthetic damage, such us the orbit and spermatic cord or pelvis and the spine [47,48]. However, carbon-ion RT is still an experimental technique, with potentially unknown late complications and due to its cost is currently available in few facilities around the world, which substantially limits its clinical utility. A retrospective case series by Greiner *et al.* (1989) described efficacy of pion irradiation in management of non-resectable RPS, applied alone or in addition to partial resection or chemotherapy [21]. However, delivered doses were substantially lower than doses

currently considered definitive, with simultaneous high frequency of mild acute enteritis and further development of late reactions in five cases. Due to lack of convincing evidence for pion radiation effectiveness in management of malignancies, interest in this this technique has gradually diminished and follow-up papers concerning usefulness of pion irradiation in RPS were not found in our review.

Limitations of this study include its retrospective character that may introduce selection bias. Moreover, with the retrospective nature of the analysis, there is a significant risk of incomplete or misinterpreted data. To reduce the risk of potential bias, all available records were reviewed independently by two co-authors. Despite that, this study and systematic review can provide valuable data due to the rarity of RPS and little available publications on the role of contemporary RT techniques in patients with primary or recurrent non-resectable/residual RPS.

Conclusions

Contemporary RT enables efficient local disease control with acceptable treatment tolerance in patients with primary or recurrent non-resectable/residual RPS. RT represents valuable treatment modality in this selected group of patients. Additional RT modalities i.e. particle therapy, MRI-guided RT or GRID/Lattice RT may be introduced to improve local control and minimize toxicity.

List Of Abbreviations

3D-RT – three-dimensional conformal radiotherapy; BT – brachytherapy; CIRT – carbon ion radiotherapy; EQD2 - equivalent 2-Gy dose; IGRT – image-guided radiotherapy; IMRT – intensity-modulated radiotherapy; MRI – magnetic resonance imaging; OAR – organ at risk; PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBE - Relative Biological Effectiveness; RECIST - Response Evaluation Criteria In Solid Tumors; RPS – retroperitoneal sarcomas; RT – radiotherapy; SBRT – stereotactic body radiotherapy; STS – soft tissue sarcomas; VMAT – volumetric modulated radiotherapy

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article (in the tables).

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

MS conceived of the presented idea. AS and MS retrieved data. AS and MS performed the literature review. AS and MS prepared the draft. AMC and PR performed quality control. AMC and PR provided critical revision of the article. MS, AS, AMC and PR discussed the concerns and contributed to the final manuscript.

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Figures

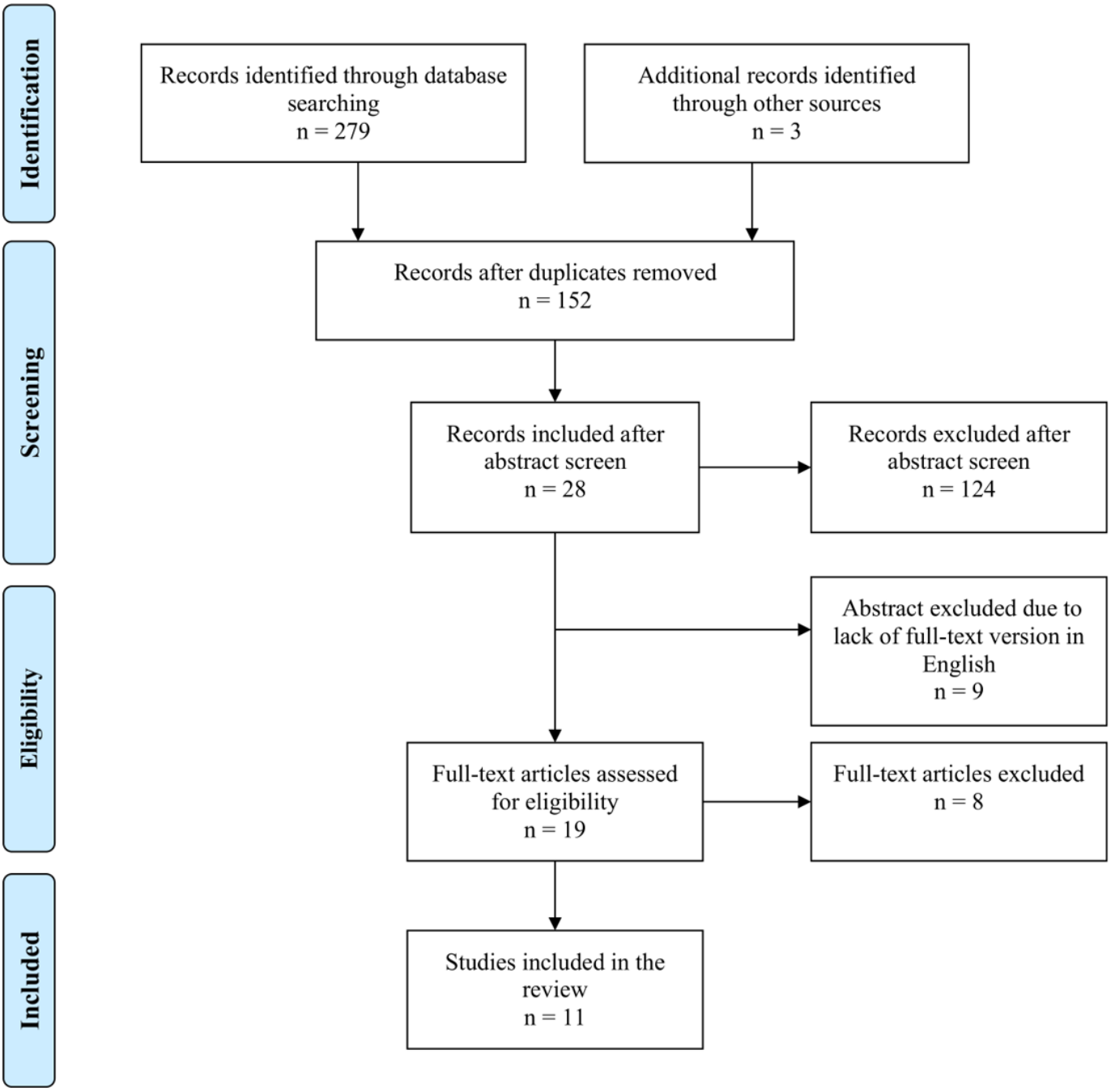

Figure 1

PRISMA flow diagram