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Dear

FREEDOM OF INFORMATION – SARCOMA MDT PRACTICE AND RADIOTHERAPY

I write in response to your request for information in relation to Sarcoma MDT Practice and Radiotherapy Planning.

Question:

1. **Treatment Consistency Across Sarcoma Typologies**
   Please provide any recorded policy, protocol, guidance, or minutes confirming whether **radiation-induced sarcomas** are **treated according to causation** (i.e. classified as one group for treatment purposes) or according to **histological typology/subtype** (e.g. angiosarcoma, leiomyosarcoma, spindle cell sarcoma, etc.).

   If no explicit policy exists, please provide any recorded correspondence or clinical governance paper where this distinction is discussed.

Answer:

Radiation induced sarcoma are treated in accordance to national and international guidelines set by the British Sarcoma Group, NCCN and ESMO. The gold standard treatment is en-bloc resection with clear margins when feasible. Systemic therapy in the advanced setting is tailored to patient factors and the soft tissue sarcoma subtype, although the majority of subtypes of radiation induced sarcoma are treated with standard STS chemotherapy.

Relating to radiotherapy treatments- Radiation induced sarcomas are treated according to causation but the histological subtype is considered, to take into account local/distant spread and prioritise the aim of the treatment. There is not a specification of when to treat with radiotherapy in our current protocols about what is the optimal treatment. Each case is assessed individually and discussed in MDT. There are retrospective reviews of the literature about radiation induced sarcomas, and treatment varies from surgery to chemotehrapy, to radiotherapy- within which a small percentage receives radical radiotherapy and a slightly larger percentage, palliative radiotherapy.

Question:

2. **Application of Cahan's Criteria and Field Geometry**

Please provide any recorded guidance, standard operating procedure, or MDT minutes that clarify:
a) Whether the terms **"arising in"** and **"occurring in"** a prior radiation field are treated as **interchangeable** in diagnostic discussions; and
b) Whether the **distance between the tumour's epicentre and the edge of the prior radiation field** is routinely measured or recorded—especially where the tumour later extends into a previously irradiated area.
Include any imaging, physics, or radiotherapy-planning documentation addressing this assessment.

Answer:

a.	Interchangeable
b.	No. We review the radiotherapy dose/volume if available. The tumour is outlined on the planning CT scan in 3D (using information from other imaging modalities where appropriate). Measurement of the tumour epicentre to the edge of prior radiation fields is an historic concept, and has been superseded in modern treatment planning software and techniques. Where possible, the previous treatment plan is reconstructed on the new CT scan to allow visual and dosimetric assessment of the combined plan. The level of accuracy of this process is dependent on how long has elapsed between the previous and current treatment, and what records of the previous treatment are available. The radiation dose received in a previous treatment is also dependent on the treatment modality and beam energy/type used at the time. Remodelling of older treatment therefore requires detailed discussion between the Clinical Oncologist and Medical Physics Expert prior to developing the new plan. The digital workflow records MPE input and decision making in each individual's patient record.

Question:

3. Reconciliation of Prior and Proposed Radiation Fields
Please provide any recorded policy, guidance, or meeting template confirming whether **previous radiation fields are routinely reconciled with proposed radiation fields** at **sarcoma MDT meetings** or during **radiotherapy planning**.
If this check is formalised (for example as a standing agenda item or pre-planning step), please provide the relevant terms of reference, procedure, or meeting record.

Answer:

As above, any previous radiotherapy is assessed with respect to any further proposed radiotherapy plan as a standard part of the radiotherapy planning process. The digital workflow

enables prior irradiation to be acknowledged and notified to the treatment planning team at the time of initial referral.

Question:

4. Constitution of the Sarcoma MDT

Please provide the current **terms of reference, membership list, or operating procedure** for your **Sarcoma MDT**, indicating:

a. Which professional disciplines are core members required to attend each meeting (e.g. surgery, clinical oncology, medical oncology, pathology, radiology, nursing).
b. Whether attendance by a **consultant surgeon** is mandatory for quoracy.
c. Whether a departmental construct such as **"Special Oncological Services (excluding surgery)"** exists within your Board's cancer governance structure, and, if so, how its remit interacts with surgical departments in MDT decision-making.

Answer:

a.	All of them The SCAN sarcoma MDT is attended by members of orthopaedic surgery, clinical oncology, medical oncology, radiology (GI and MSK), pathology, and clinical nurse specialists. Attendance from GI surgeons and plastic surgeons is sporadic due to conflicts with other clinical commitments.
b.	Yes, mandatory At least 1 orthopaedic surgeon is present at MDT for quoracy. Attendance from GI surgeons and plastic surgeons is sporadic due to conflicts with other clinical commitments. Clinical queries requiring these disciplines are normally referred and discussed offline.
c,	It is not clear to us this question - we do have oncology units for each tumoral site including sarcoma, in the oncology department. However, treatment decisions are done by direct discussion of each case in MDT in person. If any discussions need to happen between MDTs (ie emergency situations) we discuss directly in person/phone/email. Both clinical and medical oncologists manage sarcoma patients as per the national and international guidelines as aforementioned, in addition to consensus guidelines for rarer sarcoma subtypes. Referral for patients whom require surgical opinion is done via the SCAN sarcoma MDT and also to the individual surgeons offline. Clinical outcomes are set against the Quality Performance Indicators (QPIs) for sarcoma, which are reviewed at least annually across all Scottish Health Boards in the Scottish Sarcoma Network meetings.

I hope the information provide helps with your request.

If you are unhappy with our response to your request, you do have the right to request us to review it. Your request should be made within 40 working days of receipt of this letter, and we will reply

within 20 working days of receipt. If our decision is unchanged following a review and you remain dissatisfied with this, you then have the right to make a formal complaint to the Scottish Information Commissioner within 6 months of receipt of our review response. You can do this by using the Scottish Information Commissioner's Office online appeals service at www.itspublicknowledge.info/Appeal. If you remain dissatisfied with the Commissioner's response you then have the option to appeal to the Court of Session on a point of law.

If you require a review of our decision to be carried out, please write to the FOI Reviewer at the email address at the head of this letter. The review will be undertaken by a Reviewer who was not involved in the original decision-making process.

FOI responses (subject to redaction of personal information) may appear on NHS Lothian's Freedom of Information website at: https://org.nhslothian.scot/FOI/Pages/default.aspx

Yours sincerely

ALISON MACDONALD
Executive Director, Nursing
Cc: Chief Executive
Enc.

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Original Article

Radiation-Induced Sarcoma: A Retrospective Population-Based Study Over 34 Years in a Single Institution

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Abstract

Aims: About a half of all cancer patients receive radiotherapy as part of their oncological treatment. Because of the carcinogenic effect of ionising radiation, there is a rare, but definite, risk of developing secondary malignancies, including sarcomas. The aim of this retrospective study was to describe the prevalence, patient and tumour characteristics, as well as prognosis and outcome, of patients with radiation-induced sarcomas (RIS) in a cohort of patients treated in the Sarcoma Centre at Aarhus University Hospital over a period of 34 years.

Materials and methods: All patients who fulfilled the criteria for RIS and were treated for RIS in the period 1979–2013 were included. Patient data were retrieved from the Aarhus Sarcoma Registry and the National Danish Sarcoma Database, crosschecked with the National Register of Pathology and validated using the patients' medical records. The primary end point was the effect of surgery and treatment intent on overall survival. Overall survival is reported using the Kaplan–Meier estimates and compared using the Log-rank test. Descriptive statistics are presented for patients, tumours and treatment characteristics.

Results: Of 2845 patients diagnosed with sarcoma between 1979 and 2013, 64 (2%) were diagnosed with RIS. The median interval from the original malignancy was 11 years. The most common histological type was undifferentiated pleomorphic sarcoma (33%). Curative treatment was intended for 45 patients. Fifty patients underwent surgery, of whom 80% had microscopically radical resection (R0). The 5-year overall survival for the whole cohort was 32%. Patients who underwent surgery had a significantly better overall survival compared with patients who were not treated with surgery. In the univariate Cox proportional hazard analyses, no metastases at diagnosis, surgery and R0 resection were favourable prognostics factors of survival.

Conclusion: This study showed that RIS patients are unique in their epidemiology and tumour characteristics. They have a poor prognosis and need special research investigating new intensive treatment strategies to improve the outcome.

Key words: Post-irradiation sarcoma; radiation-associated sarcoma; radiation-induced sarcoma; secondary malignancies

Introduction

Radiotherapy is one of the cornerstones in the treatment of cancer. About a half of all cancer patients receive radiotherapy as part of their oncological treatment, either in a curative or palliative setting [1]. Because of the carcinogenic effect of ionising radiation, there is a risk of developing secondary malignancies, including sarcomas [2].

In 1948, Cahan *et al.* [3] were the first to describe radiation-induced sarcomas (RIS) and they proposed a series of diagnostic criteria for RIS of the bone, namely that:

(i) the tumour must arise within, or adjacent to, a previously irradiated field;
(ii) the tumour should arise at least 6 months from the cessation of radiotherapy;
(iii) histological confirmation of a sarcoma, distinct from the patient's prior malignancy, is needed.

These criteria have been modified over time, especially the duration of latency and the inclusion of soft-tissue sarcomas.

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It is estimated that the post-radiotherapy 10-year cumulative risk of developing RIS is 0.03–0.8% [4].

Because RIS arise in the previously irradiated area, there can be limited treatment options. The major limitation is that surgery of a previously irradiated area is complicated, which results in a lower resectability rate compared with sporadic sarcomas. Thijssens *et al.* [5] emphasised the low possibility of curative resection. Only 62% of patients treated with surgery had a microscopically radical resection. In a study by Neuhaus *et al.* [6], microscopically radical resection was achieved in only 37% of all patients and represented the only factor showing a significant correlation with disease-specific survival.

Another limitation of management is that radiotherapy for RIS should be administered with caution because of the higher risk of normal tissue toxicities [7].

Previous data reported 5-year survival rates between 29 and 33% [5,8–10), suggesting that RIS have a poorer prognosis compared with sporadic sarcomas. However, a recent study has indicated that the outcomes have improved, with a 5-year overall survival of 45% [11], which is still lower than what is expected in sporadic sarcoma cases. Results from our institution showed a 5-year overall survival for soft-tissue sarcomas localised in the trunk wall or extremities of 59% [12] and a 5-year overall survival for adult bone sarcoma patients of 59% [13].

Because of their rarity and diversity, RIS are seldom investigated. The aim of this retrospective study was to analyse the prevalence, patient and tumour characteristics, as well as the prognosis and outcome, of all patients with RIS who were treated at the [AQ1]XX Sarcoma Centre in the period 1979 to 2013. To the best of our knowledge, this is the first population-based study of this subject.

Materials and Methods

Patient Cohort

All children and adult patients who fulfilled Cahan *et al.*'s criteria for RIS and were treated for RIS at the Aarhus Sarcoma Centre between 1979 and 2013 were included.

Data Collection

Patient data were retrieved from Aarhus Sarcoma Registry, which is a validated database that includes data on all patients with sarcoma treated in western Denmark (population: 2.5 million) since 1979 [14] as well as from the National Danish Sarcoma Database. The National Danish Sarcoma Database was established in 2009 to include all sarcoma patients in Denmark (population: 5.7 million). Its aim is to continuously monitor and improve the quality of sarcoma management at the local and national scale [15]. When the National Database was created the Aarhus Sarcoma Registry became part of it. Therefore, there is no overlap between the two databases.

Information regarding age, gender, antecedent malignancies or benign conditions, latency from the diagnosis of the original cancer to the diagnosis of the RIS, clinical presentation (localisation, tumour size, metastases at presentation), histological diagnoses and malignancy grade, treatment modalities (surgery, chemotherapy, radiotherapy or combinations of these treatments) and overall survival was obtained.

Tumour localisations were divided into the following anatomical groups:

- breast and/or the chest wall
- pelvis including the pelvic wall and the intrapelvic organs
- head and neck: from the clavicles to the scalp
- extremities: upper extremity included the arms and the shoulders with the scapula region and clavicle. Lower extremity included the area from the hip to the toes
- no tumours were located in the region of the abdomen.

The surgical margin was categorised either as intralesional (R1) or as microscopically complete (R0) including radical, wide and marginal resection.

The clinical data obtained from the Aarhus Sarcoma Registry and the National Danish Sarcoma Database were validated by investigating the patients' medical records and by cross-checking with data from the National Register of Pathology.

Statistics

The primary end point of the study was overall survival, which was calculated from the date of diagnosis of RIS until death of any cause.

Descriptive statistics were applied to present the patient, tumour and treatment characteristics. The study period ended on 31 December 2018 and the patients alive at that date were censored. Kaplan–Meier plots were used to illustrate overall survival. Overall survival estimates were compared using the Log-rank test. The crude analysis was carried out using the univariate Cox proportional hazard model. Because of the small number of patients and the low number of events, the data were not suitable for multivariate analysis.

Ethics

The Ethics Committee of Denmark (1-10-72-233-12) and the Danish Agency of Data Protection (1-16-02-677-15) have approved the study.

Results

In the Aarhus Sarcoma Registry, 59 sarcomas were registered as RIS. However, a thorough evaluation of the medical and pathology records identified five patients not fulfilling Cahan *et al.*'s criteria and they were excluded. In the National Danish Sarcoma Database, it is not registered

whether a sarcoma is radiation-induced or not. In total, 58 patients were registered with at least one previous solid tumour as a comorbidity. By going through the medical and pathology records of these patients, we identified 10 cases that met the criteria for RIS. In the end, of 2845 patients diagnosed with all kinds of sarcoma in the designated period, 64 patients (2%) with RIS were identified (Figure 1).

The clinicopathological characteristics are summarised in Table 1. Irrespective of the original tumour type, the median latent interval from original malignancy was 11 years (5th to 95th percentile: 3–36 years). For patients with original breast cancer, the median latent interval was 9 years (5th–95th percentile: 4–33), whereas for the rest of the group it was 14 years (5th–95th percentile: 2–40). Original breast cancer accounted for 31 (48%) and of these 19 had RIS in the breast region and 12 patients developed RIS either in the proximal upper extremity or scapular region. Regardless of original malignancy, the most common histological type of RIS was undifferentiated pleomorphic sarcoma (21/64) followed by angiosarcoma (16/64) and osteosarcoma (7/64).

Fifty patients (of 64) were treated surgically. Of these, 12 had angiosarcoma of the breast. Of these 50 operated patients, wide margin resection was achieved in 36 (36/50), R0 resection (wide and marginal margin) was achieved in 40 (40/50), R1 resection was achieved in seven (7/50), whereas it was not possible to define the surgical margin in the remaining three patients.

Doxorubicin-based chemotherapy was given to 11 patients, but only three of them (all with osteosarcoma) were treated with curative intent. All three patients who underwent curative chemotherapy were also operated on as part of their treatment.

Eight patients were treated with radiotherapy, but only one patient was treated with curative intent, receiving 55 Gy in 23 fractions.

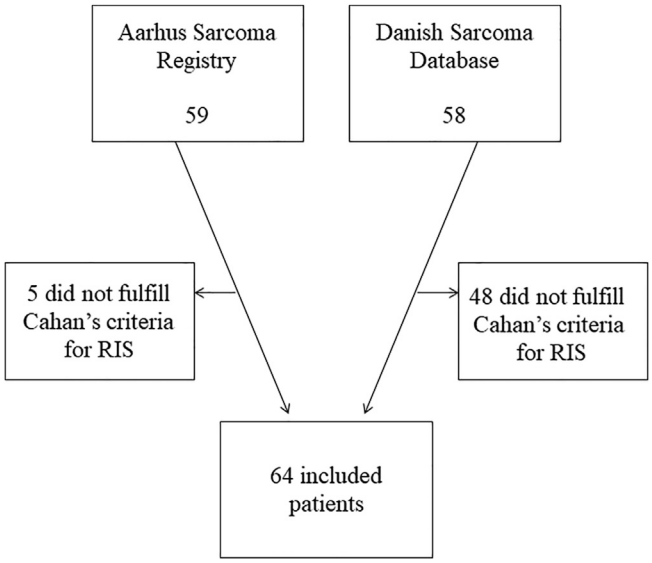

Fig 1. Patient inclusion and exclusion.

Table 1
Clinicopathological characteristics

	n	%*
Gender		
Female	53	83
Male	11	17
Age at original cancer†	46 (14–77)	
Age at RIS‡	67 (29–82)	
Latency§	11 (3–36)	
Original tumour localisation		
Breast or chest wall	31	48
Pelvis	16	25
Head and neck	10	16
Extremities	7	11
RIS localisation		
Breast or chest wall	19	30
Extremities	19	30
Pelvis	16	25
Head and neck	10	16
RIS histology		
Soft-tissue sarcoma	49	77
UPS	16	
Angiosarcoma	16	
Leiomyosarcoma	4	
Other‖	13	
Bone sarcoma	15	23
UPS	5	
Chondrosarcoma	3	
Ewing/osteosarcoma	7	
RIS grade		
Low	3	5
Intermediate	6	9
High	47	73
Unknown	6	9
Missing data	2	3
RIS tumour size¶	8 (2–30)	
Metastasis at presentation of RIS		
No	50	78
Yes	14	22
Treatment of RIS		
Surgery	44	69
Surgery + radiotherapy/chemotherapy	6	9
Non-surgical treatment	10	16
No treatment	4	6
Surgical margin		
No surgery	14	22
Intralesional (R1)	7	11
Wide/marginal (R0)	40	63
Missing data	3	5
Treatment intent		
Curative	45	70
Palliative	19	30

RIS, radiation-induced sarcoma; UPS, undifferentiated pleomorphic sarcoma.
Age at original cancer is reported as median age in years with 5–95 percentile.

* Percentage may not total 100 due to rounding.

† Age at original cancer is reported as median age in years with 5–95 percentile.

‡ Age at diagnosis of RIS is reported as median age in years with 5–95 percentile.

§ Latency is reported as median years from diagnosis of original cancer until diagnosis of RIS with 5–95 percentile.

‖ Including dermatofibrosarcoma, epithelioid sarcoma, fibrosarcoma, liposarcoma, malignant peripheral nerve sheath tumour, malignant schwannoma, rhabdomyosarcoma.

¶ Tumour size of RIS is reported as median size in cm with 5–95 percentile.

The median follow-up in all patients was 1.7 years (range: 0.1–34 years). The median follow-up in patients still alive at the time of analysis was 9 years (range: 2.2–34 years). Forty-three patients had died by 5 years. The median overall survival in all patients was 1.5 years (95% confidence interval: 1.0–4.1 years) and the 5-year overall survival was 32% (95% confidence interval: 20–44%) (Figure 2). For patients with RIS in the extremities, breast/chest wall, pelvic region and head and neck, the median overall survival was 8.8 years (95% confidence interval: 0.95–25.8), 3.2 years (95% confidence interval: 0.9–8.3), 0.9 years (95% confidence interval: 0.3–8.0) and 0.9 years (95% confidence interval: 0.5–2.0), respectively.

The results of the treatment were described as 'complete remission' in 45 patients (70%). Patients treated with curative intent had a significantly better survival (Figure 3). Because the curative treatment strategy almost always included surgery, patients who underwent surgery had a significantly better overall survival (Figure 4). The median overall survival for patients treated with surgery was 2.7 years (95% confidence interval: 1.2–5.7 years) and the 5-year overall survival was 39% (95% confidence interval: 25–52%). The median overall survival for patients who underwent surgery with an R0 resection was 4.5 years (95% confidence interval: 2.0–11.3 years), compared with a median overall survival of 0.5 years (95% confidence interval: 0.3–2.0 years) for patients who underwent surgery with R1 resection. The median overall survival for patients not treated with surgery was 0.9 years (95% confidence interval: 0.4–1.4 years) and the 5-year overall survival was 7.1% (95% confidence interval: 0.5–28%).

In the univariate Cox proportional hazard analysis, no metastases at diagnosis, surgery and R0 resection were favourable prognostic factors of survival (Table 2).

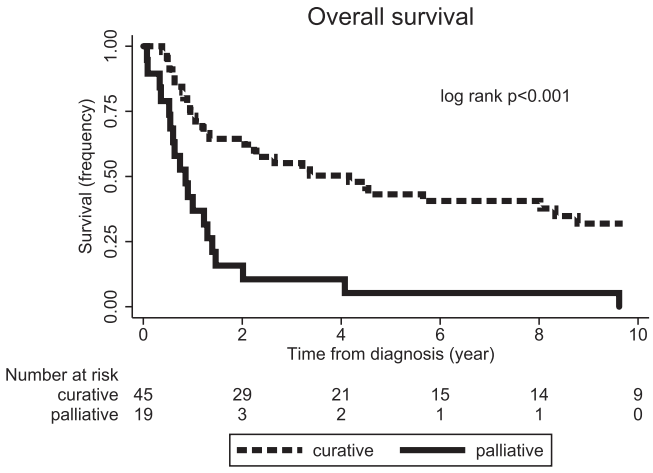

Fig 3. Overall survival according to treatment intent.

Discussion

Comparison with Existing Literature on Radiation-induced Sarcoma

The clinicopathological characteristics of the patients in this study were comparable with the existing literature.

In previous studies, the median age at which the patient had their original cancer ranged from 41 to 44 years [5,10,11,16], which is not different from the 46 years of age reported in the present study. However, the median age of 67 years at the time of RIS presented in this study is higher than in most published literature (median age 52–59 years) [4,5,10,11,16,17]. This difference may not be clinically relevant as the median time from the diagnosis of original cancer to RIS in our study (11 years) is similar to the 8–14 years reported in other studies [5,8–11,16–18].

In our study, 83% of RIS patients were women. A similar finding has been reported in other studies [8–11] and explained by the frequency of radiotherapy for the management of breast cancer, a common disease among women

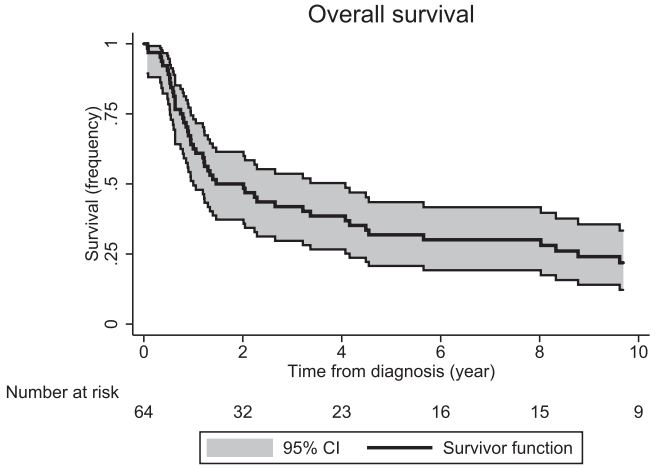

Fig 2. Overall survival for all patients.

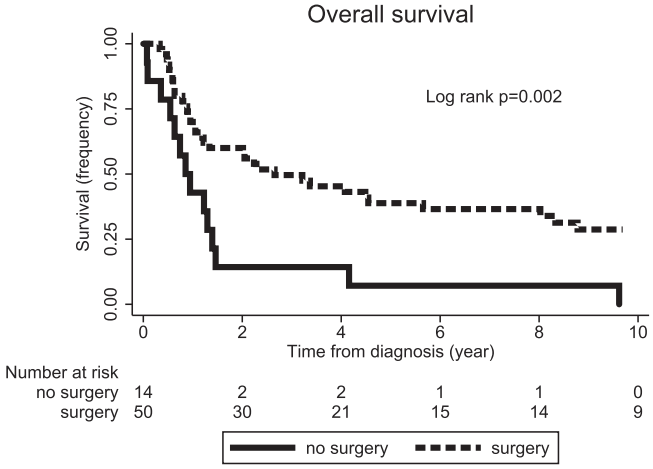

Fig 4. Overall survival according to surgery.

Table 2
Univariate analyses for overall survival for all patients

	Hazard ratio	95% confidence interval	*P* value
RIS localisation			
Breast or chest wall	1		
Pelvis	2.3	[1.1; 4.7]	**0.03**
Extremities	0.6	[0.3; 1.3]	0.20
Head and neck	1.6	[0.7; 3.7]	0.26
Metastasis at presentation			
No	1		
Yes	2.4	[1.3; 4.7]	< **0.01**
Treatment intent			
Curative	1		
Palliative	3.5	[1.9; 6.4]	< **0.01**
Surgery			
Surgery	1		
No surgery	2.7	[1.4; 5.0]	< **0.01**
Margin			
Wide/marginal (R0)	1		
Intralesional (R1)	3.6	[1.8; 7.1]	< **0.01**
No surgery	5.1	[2.1; 12.4]	< **0.01**

RIS, radiation-induced sarcoma.
The significant p-values are in bold ($p \leq 0.05$).

that is frequently cured with standard therapeutic approaches [19]. Accordingly, breast cancer was the most frequent original cancer in our study as well as in literature data [5,10,11,16,17].

The frequency of different histological subtypes varies from study to study. However, undifferentiated pleomorphic sarcoma, as in our study, and osteosarcoma are the most common histological subtypes [5,8–11,16,17,20]. Similar to our study, most RIS were described in the literature to be of high grade [8,10,20] and we documented that one fifth of the patients had metastatic disease at the time of RIS. Comparable results were reported in other studies [9,10,17].

Studies have shown that patients who were treated with surgery have a better chance of survival compared with patients who did not undergo surgery [5,10,11,16]. In our data, 70% of all included patients were treated with curative intent. This is in accordance with the results by Kim *et al.* [11], who found that 58% of RIS were treated with curative intent. As in similar studies, we found that the preferred treatment modality was surgery [5,10,11]. Also, R0 resection was obtained in 80% of all patients treated with surgery. The proportion of radical resections varies markedly from 46 to 95% between different studies [5,10,11]. The great variation could be explained by differences in the selection of patients for surgery and the fact that the studies described different time periods.

Because RIS by definition arises in previously irradiated areas, many clinicians would be reluctant to reirradiate the patients because of toxicity concerns [5,11]. Thirteen per cent of the patients in our study were treated with reirradiation therapy, but only one patient was treated with a high radiation dose with curative intent. De Jong *et al.* [21] found that reirradiation combined with hyperthermia is a feasible treatment for RIS in patients with thoracic RIS, showing promising response and local control rates.

The role of chemotherapy in RIS has not been established but has been used in the neoadjuvant, adjuvant and palliative settings [5,11,16,17,20,22].

The 5-year overall survival of 32% in our study is similar to the survival reported in comparable studies [5,8–10]. More recent studies, such as Kim *et al.* [11], reported a 5-year overall survival of 45% at a large single centre in Korea between 2000 and 2014. The improved survival in this recent study could be explained by the introduction of modern surgical and radiotherapy treatment techniques.

In our study, RIS accounted for 2% of all sarcomas. This is in line with the existing literature showing that RIS accounts for up to 3% of all sarcomas [6,10,11,23].

Comparison with Sporadic Sarcoma

Aggerholm-Pedersen *et al.* [13] and Maretty-Nielsen *et al.* [12] have published data on sporadic sarcoma from the same database as in our study. Table 3 shows a comparison of sporadic sarcoma and RIS. The age difference can be explained by the fact that RIS occurs secondary to the treatment of another malignancy with a latency of several years. Metastasis at the time of diagnosis was more frequent in RIS, which could indicate that RIS is more likely to metastasise or has longer latency to diagnosis. Thus, the clinicopathological factors for RIS differed from that of sporadic sarcoma. RIS is also known to have a worse prognosis than sporadic sarcoma. Bjerkehagen *et al.* [9] investigated the question of whether previous radiotherapy is a worse prognosticator. In their analysis, a previous radiotherapy history was not a prognostic factor, but unlike sporadic sarcoma, RIS tended to occur in a central location and to be associated with incomplete surgery, which are known to be poor prognosticators in sarcoma. In contrast to Bjerkehagen *et al.* [9], we found that the proportion who underwent wide margin resection in our centre was comparable in RIS

Table 3
Comparison of clinicopathological characteristics for radiation-induced sarcoma, sporadic bone and soft-tissue sarcoma

	Radiation-induced Sarcoma ($n = 64$)	Sporadic bone sarcoma [13] ($n = 453$)	Sporadic soft-tissue sarcoma [14] ($n = 1246$)
Gender			
Female	83%	40%	47%
Male	17%	60%	53%
Age at diagnosis*	67	46	58
High-grade tumours	73%	61%	69%
Metastasis at presentation	22%	15%	12%
Surgery	78%	86%	94%
Wide margin resection (operated patients only)	72%	72%	65%
Wide margin resection (all patients)	56%	59%	60%

* Age at diagnosis is reported as median age in years.

and sporadic sarcomas. It is possible that the differences in clinicopathological factors and survival between RIS and sporadic sarcoma could, in part, be explained by differences in biology. It has been reported that some genetic changes, such as MYC amplification, are more often seen in RIS compared with sporadic sarcomas [24–29]. In some cases, these specific changes are known to be associated with poor prognosis [24].

Strengths and Limitations

A major strength of our study is the size of the series and that it was population based and had a long follow-up. An important limitation is the lack of a control group of spontaneous sarcomas.

Future Research

The low 5-year overall survival of 32% suggests that a future trial should explore a strategy such as an intensified preoperative chemotherapy to facilitate radical surgery, which seems to be essential to improve survival. In addition, future studies are needed to explore the biology of RIS to be able to target the treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2020.12.009.

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Systematic Review

Treatment and Outcomes of Radiation-Induced Soft Tissue Sarcomas of the Extremities and Trunk—A Systematic Review of the Literature

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Simple Summary: Radiation-induced soft tissue sarcomas (RISs) are rare cancers with a dire prognosis caused by past radiation therapy. Due to their low recurrence, they are poorly understood. The aim of this systematic review was to analyze how RIS is treated, and the outcomes that patients face. After reviewing 21 studies with 1371 RIS patients, it was found that surgery was the most common treatment, with chemotherapy and radiotherapy used less frequently. The most common histological type was undifferentiated pleomorphic sarcoma (42.2%). Patients with RIS had a 5-year survival rate of 45% and high rates of local recurrence (39%) and cancer spreading (27%). These findings shed light on the challenges of managing RIS and may guide future research to improve treatment outcomes for these patients.

Abstract: Introduction: Radiation-induced soft tissue sarcomas (RISs) are rare secondary malignancies with a dire prognosis. The literature on the management of these tumors remains scarce due to their low incidence. Our systematic review sought to assess the treatment alternatives and outcomes of patients with RIS. Methods: A systematic review was conducted following the PRISMA guidelines. Our study was registered in PROSPERO (ID: CRD42023438415). Quality assessment was performed using the STROBE checklist. Weighted means for both continuous and categorical values were calculated. Results: Twenty-one studies comprising 1371 patients with RIS were included. The mean latency period from radiation to RIS diagnosis was 14 years, and the mean radiation dose delivered to the primary malignancy was 29.2 Gy. The most common histological type was undifferentiated pleomorphic sarcoma (42.2%), and 64% of all tumors were high-grade. The trunk was the most common location (59%), followed by extremities (21%) and pelvis (11%). Surgery was performed in 68% of patients and, among those with an appendicular tumor, the majority (74%) underwent limb-salvage surgery. Negative margins were attained in 58% of patients. Chemotherapy and radiotherapy were administered in 29% and 15% of patients, respectively. The mean 5-year overall survival was 45%, and the local recurrence and metastasis rates were 39% and 27%, respectively. Conclusions: In our study, the most common treatment was surgical resection, with RT and chemotherapy being administered in less than one third of patients. Patients with RIS exhibited poor oncologic outcomes. Future studies should compare RIS with de novo STS while controlling for confounders.

Keywords: radiation-associated sarcoma; soft tissue sarcoma; surgery; survival

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1. Introduction

Radiation-induced soft tissue sarcomas (RISs) are a devastating late complication of radiation therapy (RT). These neoplasms, which can originate in the bone or soft tissue, were first defined by Cahan et al. in 1948 [1]. In their study, they established the following diagnosis criteria: (1) history of radiation therapy; (2) occurrence of the sarcoma within a previously irradiated field; (3) asymptomatic latency period of several years; and (4) histologic confirmation of sarcomatous nature of the post-irradiation lesion [1]. With a 15-year cumulative incidence of 3.2 per 1000 people that have received RT, RISs are a rare group of neoplasms [2]. Nonetheless, incidence of RIS is increasing due to the longer survival of oncologic patients and more extensive use of RT within this population [3].

RISs typically present as large, high-grade tumors, and exhibit poorer oncologic outcomes compared to de novo soft tissue sarcomas (STSs) [4–8]. The management of RIS is similar to that of de novo STS and consists of surgical resection, with or without neoadjuvant chemotherapy (QT). The role of RT in RIS, however, remains unclear due to potential side effects of reirradiation [9]. Due to the condition's low incidence, comprehensive studies on the optimal treatment of RIS are scarce. Notably, there have been no large prospective studies or randomized controlled trials on the topic and the largest study currently available includes only 510 patients with RIS [10]. Moreover, the majority of the RIS literature primarily focuses on tumors arising in the chest wall after the irradiation of breast carcinoma [2,5,7,11,12]. To our knowledge, there have been no systematic reviews assessing the oncologic outcomes in this population.

In our systematic review, we sought to answer the following questions: (1) what are the demographic and clinical characteristics of patients with RIS? (2) What are the most common treatment strategies of patients with RIS? (3) What are the oncologic outcomes of patients with RIS?

2. Materials and Methods

2.1. Search Strategy

A comprehensive search of the PubMed and Embase libraries was conducted on 10 September 2023. The following terms and Boolean operators were used: ("radiation-induced" OR "radiation-associated" OR "post-irradiation" OR "postirradiation" OR "post-radiation" OR "postradiation") AND sarcoma AND (bone OR soft tissue). In addition, we reviewed all included studies to identify references that may have been missed in our initial search. Our systematic review was registered in PROSPERO (ID: CRD42023438415).

2.2. Eligibility Criteria

To be included in our study, articles had to (1) report oncologic outcomes of RIS located in the extremities, trunk or pelvis, and (2) include at least ten patients diagnosed with an RIS in the aforementioned locations. Non-peer-reviewed publications and studies not written in English, Spanish, German, Italian or Portuguese were excluded.

2.3. Selection, Data Collection and Extraction

A separate search query for each of the two databases used (PubMed and Embase) was performed. The results were then uploaded into Covidence™ (Veritas Health Information) and duplicates were removed. Three reviewers (M.L.I., K.K.L. and G.A.S.) independently screened studies for eligibility. In case of disagreement, the senior author (J.P.M.) was consulted, and the final decision was reached by consensus.

Data from the included manuscripts were extracted into a pre-assembled spreadsheet. The following variables were retrieved: first author, year of publication, study design, country and institution where the study was performed, age and sex of patients, latency time and radiation dose (Gy), primary tumor radiated, follow-up, tumor location, tumor grade and size, histology, treatment characteristics and oncologic outcomes. Treatment variables retrieved included the percentage of patients receiving surgical management for RIS and the negative margin rate. For RIS located in the extremities, the type of surgery was

classified as a limb-salvage surgery or amputation. RT and QT treatment strategy variables included both neoadjuvant and adjuvant therapies, given that most studies did not specify the distinction.

For continuous variables like age and follow-up time, we collected mean or median values based on the reported metric used by the author. We evaluated three oncologic outcomes: five-year overall survival, local recurrence rate and metastasis rate. Five-year overall survival was determined based on the Kaplan–Meier estimates reported by each study. We defined local recurrence as the presence of tumoral tissue in the vicinity of the former RIS tumor bed or at the end of the amputation stump. Local recurrence and metastasis rates were calculated as the proportion of patients who experienced the event of interest at their last follow-up. We chose these outcomes because they were the most frequently reported in the included studies.

2.4. Study Selection and Characteristics

This systematic review followed the PRISMA guidelines. The search resulted in 1342 titles in PubMed and 525 titles in EMBASE, and the resulting datasets were exported to Covidence™ (Veritas Health Information). After duplicate removal, three independent reviewers (M.L.I., K.K.L. and G.A.S.) screened all titles and 1620 studies were excluded (Figure 1). The full manuscripts of 153 studies were then reviewed and a total of 22 articles met our inclusion criteria and progressed to quality assessment.

2.5. Quality Assessment

We evaluated study quality using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. We employed 10 out of the 22 checklist items, consistent with prior orthopedic literature [13–16]. Each item received a score from 0 to 2, where well-described items earned 2 points, partly described items received 1 point and poorly described items obtained 0 points. Studies with a cumulative score of $\geq$15 points were considered for inclusion. We excluded 1 study due to a low score [17] and 21 studies were finally included in our systematic review (Figure 1).

2.6. Caracteristics of Included Studies

A total of 1371 patients with radiation-induced sarcomas from 21 studies were included in our systematic review [3–12,18–28]. The number of patients included ranged from 10 [18] to 510 [10] (Table 1). The majority of studies were performed in the United States and all articles were retrospective cohorts (Supplementary Table S1). Date of publication of included studies ranged from 1986 [22] to 2023 [11].

Table 1. Demographic characteristics of included patients.

Author	RIS (*n*)	Age (Years) $^{\alpha}$	Sex (M:F)	Latency (Years) $^{\alpha}$	Dose (Gy) $^{\alpha}$	FU (Months) $^{\alpha}$
Kao et al. [11]	57	60 $^{+}$	0.57 $^{+}$	13 $^{+}$		28.3 $^{+}$
Spalek et al. [3]	49	57 $^{+}$	2.87 $^{+}$		11 $^{\Phi+}$	
Callesen et al. [20]	49	67 $^{+}$	0.21 $^{+}$	11 $^{\Phi+}$		20.4 $^{\Phi+}$
Italiano et al. [10]	510	66	0.24 $^{+}$			62.9
Joo et al. [26]	19	56	0.58 $^{+}$	19.5	43.4 $^{\Phi}$	25 $^{\Phi}$
Dineen et al. [23]	55	59 $^{\Phi+}$	0.67 $^{+}$	9.33 $^{\Phi+}$	50 $^{\Phi+}$	
Kim et al. [27]	12	48	0.20	12.1 $^{\Phi+}$	50.4 $^{\Phi+}$	23.1 $^{\Phi+}$
Riad et al. [4]	44	56 $^{\Phi+}$	0.69	45 $^{\Phi}$	12.4	29 $^{\Phi}$
Gladdy et al. [5]	108	58.5 $^{\Phi+}$	0.73	10 $^{+}$	10 $^{+}$	26.7 $^{\Phi}$
Neuhaus et al. [12]	54	58 $^{\Phi+}$		11 $^{\Phi+}$	50 $^{\Phi+}$	53 $^{\Phi+}$
Holt et al. [24]	38	33	0.73 $^{+}$	15.4	15.4	23
Thijssens et al. [7]	15	59	0.07	55.5	10.8	26.6
Cha et al. [21]	64	62 $^{+}$	0.86 $^{+}$	8.6 $^{\Phi+}$		36 $^{\Phi+}$
Fang et al. [6]	14	58.4	0.08	12.6	12.6	24

Table 1. *Cont.*

Author	RIS (*n*)	Age (Years) $^{\alpha}$	Sex (M:F)	Latency (Years) $^{\alpha}$	Dose (Gy) $^{\alpha}$	FU (Months) $^{\alpha}$
Lagrange et al. [9]	56	55.5	0.27	13.3	13.3	38.8
Inoue et al. [25]	11	28.7 $^{+}$	0.59 $^{+}$	17 $^{+}$		
Bloechle et al. [18]	10	51.1	0.11	15.8	39.9	56.4
Brady et al. [19]	113	41 $^{+}$	0.90 $^{+}$	10.3 $^{+}$	50 $^{\Phi+}$	37 $^{+}$
Wiklund et al. [8]	20	63	0.10		13.5	44.4
Laskin et al. [28]	53	51	0.39	9.6	38.6	23.6
Davidson et al. [22]	20	35.5		16.8 $^{\Phi+}$	37.3	

FU: follow-up; RIS: radiation-induced soft tissue sarcoma. $^{\alpha}$ values in this column refer to the mean. $^{\Phi}$ values in these cells refer to the median. $^{+}$ calculated from entire study sample and not restricted to RIS located in the appendicular skeleton, pelvis or trunk.

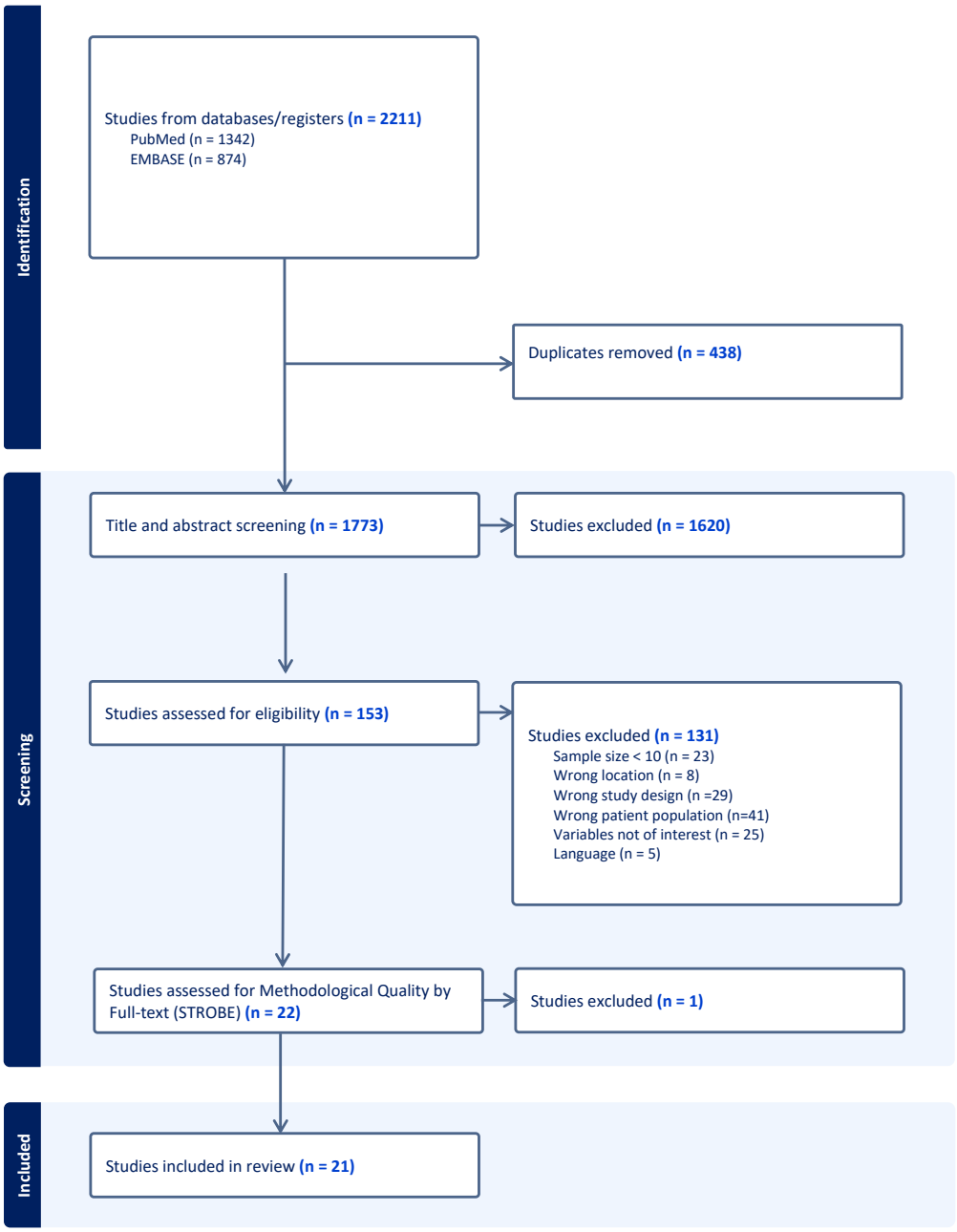

Figure 1. PRISMA flowchart for our literature search and selection of relevant articles.

3. Data Analysis

Continuous variables were displayed as mean or median values, depending on the metric used by the study. Categorical variables were reported as proportions, which we calculated by dividing the total events of interest by the overall at-risk population. Weighted means for both continuous and categorical values were calculated in order to adjust for the sample size of each study. All analyses were performed using Microsoft Excel version 16.73 (Microsoft Corp., Albuquerque, NM, USA) and StataSE 14 (StataCorp., College Station, TX, USA).

4. Results

4.1. What Are the Demographic and Clinical Characteristics of Patients with RIS?

A total of 1371 patients with RIS were included with a mean age of 58 at diagnosis, ranging from 28.7 [25] to 67 [20], a male: female ratio of 0.57 and a follow-up ranging from 20.4 [20] to 62.9 months [10]. The mean latency between the primary tumor and the RIS was 14.1 years and ranged from 8.6 [21] to 55.5 years [7]. The mean radiation dose received for the primary malignancy was 29.2 Gy and ranged from 10 [5] to 50.4 Gy [27]. The most common location was the trunk (59%), followed by extremities (21%) and pelvis (11%) (Table 2). The mean tumor size was 6.13 cm and 64% of RISs were high-grade. Regarding RIS histology, the most common histologic subtypes were undifferentiated pleomorphic sarcoma (UPS) and angiosarcoma (AS), occurring in 42.2 and 25.6% of cases, respectively (Figure 2).

Table 2. Clinical characteristics of included patients.

Author	Location			High Grade (%)	Size (cm) $^{\alpha}$	Histology
	Trunk (%)	Extremity (%)	Pelvis (%)			
Kao et al. [11]	82%	18%	0%	66% $^{+}$	7.4 $^{+}$	UPS (45%), AS (23%), MPNST (14%), LMS (12%), RS (4%)
Spalek et al. [3]	57% $^{++}$	14% $^{++}$	29% $^{++}$	95%		UPS (30%), AS (14%), MFS (12%), MPNST (8%), other (24%)
Callesen et al. [20]	57%	13%	30%	73%$^{+}$	8 $^{\Phi+}$	UPS (48%), AS (25%), Ewing sarcoma (11%), LMS (6%) $^{+}$
Italiano et al. [10]	58%	16%	10%	43%	5.5	AS (38%), UPS (34%), other (28%)
Joo et al. [26]	21%	26%	26%	94%	5.7	FS (42%), AS (17%), UPS (17%), other (24%)
Dineen et al. [23]	76%	24%	0%		6 $^{\Phi}$	UPS (100%)
Kim et al. [27]					4.8 $^{\Phi+}$	UPS (33%), AS (6%), CS (3%), other (58%) $^{+}$
Riad et al. [4]	20%	80%	0%	70%	7.1	UPS (36%), AS (18%), LS (9%), other (37%)
Gladdy et al. [5]	74%	26%	0%	83%$^{+}$	5.7^{+}	UPS (34%), AS (21%), LMS (12%), FS (12%)
Neuhaus et al. [12]	74%	9%	17%	87%$^{+}$	8^{+}	LMS (28%), UPS (16%), AS (13%) $^{+}$
Holt et al. [24]						UPS (36%), OS (28%), LMS (6.4%), RMS (4.3%)
Thijssens et al. [7]	80%	0%	20%	40%		AS (40%), UPS (40%), FS (13%), pleomorphic LMS (7%)
Cha et al. [21]	60%	40%	0%	79%$^{+}$	≤5 cm: 40% >5–10 cm: 37% >10 cm: 23%	UPS (23%), FS (15%), AS (15%), LMS (12%) $^{+}$
Fang et al. [6]	50%	14%	36%	100%	7.8	UPS (50%), EOS (43%), FS (7%)
Lagrange et al. [9]	46%	10%	16%	55% $^{+}$		UPS (43%) AS (12%) OS (9%), FS (11%) $^{+}$
Inoue et al. [25]	0%	27%	73%	74% $^{+}$	9 $^{+}$	FS (62%), UPS (25%), other (13%) $^{+}$
Bloechle et al. [18]	50%	40%	10%	50%	6.2	UPS (60%), HS (20%)
Brady et al. [19]				87% $^{+}$	6 $^{+}$	OS (21%), UPS (16%), AS/LA (15%) $^{+}$
Wiklund et al. [8]	50%	15%	35%	100%	8.8	UPS (30%), EOS (20%), FS (20%), LMS (15%), MS (5%), AS (5%)
Laskin et al. [28]	69%	17%	14%			UPS (77%), FS (9%), EOS (6%), MS (6%), Others (2%) $^{+}$
Davidson et al. [22]						UPS (40%), FS (20%), LA (10%), EOS (10%)

AS: angiosarcoma; CS: chondrosarcoma; EOS: extraskeletal osteosarcoma; FS: fibrosarcoma; HS: hemangiosarcoma; LA: lymphangiosarcoma; LMS: leiomyosarcoma; LS: liposarcoma; MS: malignant schwannoma; MPNST: malignant peripheral nerve sheath tumor; OS: osteosarcoma; RMS: rhabdomyosarcoma; UPS: undifferentiated pleomorphic sarcoma. $^{\alpha}$ values in this column refer to the mean; $^{\Phi}$ values in these cells refer to the median. $^{+}$ calculated from entire study sample and not restricted to RIS located in the appendicular skeleton, pelvis or trunk; $^{++}$ value inferred from proportions.

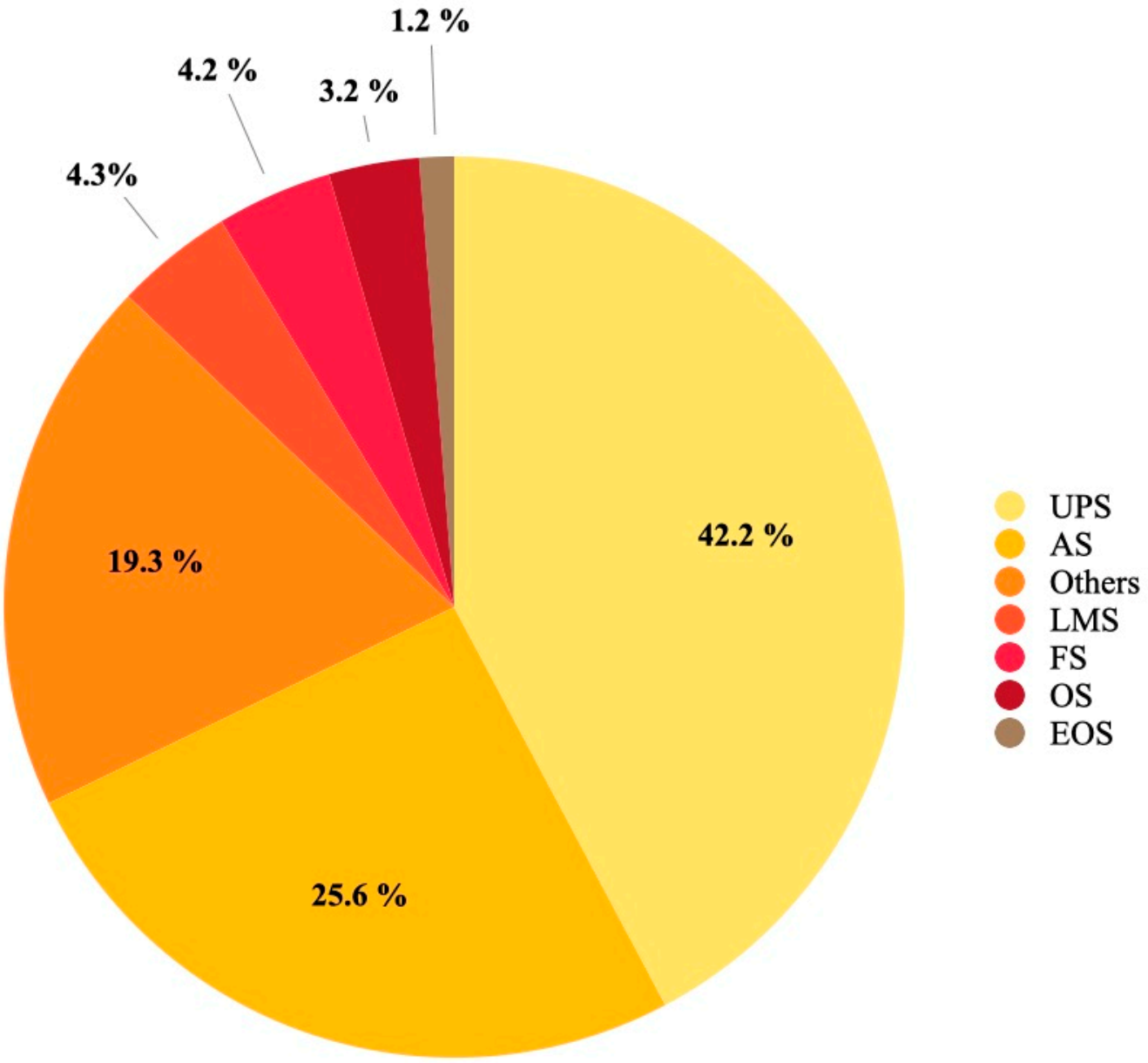

Figure 2. Pie chart of the histology distribution of the included RISs. UPS: undifferentiated pleomorphic sarcoma; AS: angiosarcoma; LMS: leiomyosarcoma; FS: fibrosarcoma; OS: osteosarcoma; EOS: extraskeletal osteosarcoma; others: malignant peripheral nerve sheath tumor, pleomorphic leiomyosarcoma, myxofibrosarcoma, Ewing sarcoma, malignant schwannoma, rhabdomyosarcoma, hemangiosarcoma, lymphangiosarcoma.

4.2. What Are the Most Common Treatment Strategies of Patients with RIS?

Surgical resection was conducted in 68% of patients, with values ranging from 45% [25] to 100% [5] (Table 3). The majority of patients (74%) with appendicular RIS underwent limb-salvage surgery and 26% of them had an amputation as the primary procedure. Negative margins were reported in 58% of patients, with the rate ranging from 31% [3] to 90% [18]. QT, both neoadjuvant and adjuvant, was administered to 29% of patients, with values ranging from 0% [18] to 88% [3]. RT for the management of RIS was only described in 10 studies and it was performed in 15% of patients, with values ranging from 0% [12,18] to 53% [11].

Table 3. Treatment strategies of included patients.

Author	Surgery	Type of Surgery		Negative Surgical Margins	(Neo)-Adjuvant RT	(Neo)-Adjuvant QT
		Limb-Salvage Surgery	Amputation			
Kao et al. [11]	66% +			43% +	53% +	47% +
Spalek et al. [3]	67% +			31% +	33%	88% +
Callesen et al. [20]	78% +			80% +	9% +	9% +
Italiano et al. [10]	53%				9%	31%
Joo et al. [26]	94%	95%	5%	74% +		52%
Dineen et al. [23]						
Kim et al. [27]	100%				16%	25%
Riad et al. [4]	95%	86%	14%	83%	30%	18%
Gladdy et al. [5]	100% +			69% +	22% +	18%
Neuhaus et al. [12]	72% +			75% +	0%	9% +
Holt et al. [24]						
Thijssens et al. [7]	67%	40%	60%	60%	7%	13%
Cha et al. [21]	90% +			47% +		20% +
Fang et al. [6]	93%					
Lagrange et al. [9]						
Inoue et al. [25]	45% +	20%	80%			
Bloechle et al. [18]	100%	90%	10%	90%	0%	0%
Brady et al. [19]				42% +		
Wiklund et al. [8]						
Laskin et al. [28]						
Davidson et al. [22]						

QT: chemotherapy; RT: radiation therapy. + calculated from entire study sample and not restricted to RIS located in the appendicular skeleton, pelvis or trunk.

4.3. What Are the Oncologic Outcomes of Patients with RIS?

The five-year overall survival was 45% among included studies, with values ranging from 13% [7] to 68% [25] (Table 4). At the last follow-up, 39% of patients had local recurrence, with values ranging from 20% [11] to 65% [12]. Metastasis occurred in 27% of patients with RIS, with reported rates ranging from 5% [8] to 67% [7].

Table 4. Oncologic outcomes of included patients.

Author	5y OS	Local Recurrence (% of Total)	Metastasis Rate (% of Total)
Kao et al. [11]	42% +	20%	9%
Spalek et al. [3]	17%	31% +	28% +
Callesen et al. [20]	32% +		22% +
Italiano et al. [10]	53%		
Joo et al. [26]	50%	26%	
Dineen et al. [23]	47%	58%	
Kim et al. [27]	45% +	47% +	37% +
Riad et al. [4]	44%	26%	50%
Gladdy et al. [5]			
Neuhaus et al. [12]	45% +	65% +	44% +
Holt et al. [24]	51%		
Thijssens et al. [7]	13%	40%	67%
Cha et al. [21]	41% +	47% +	28% +
Fang et al. [6]	53%	30%	20%
Lagrange et al. [9]	35%	30%	52%
Inoue et al. [25]	68% +		
Bloechle et al. [18]	40%		10%
Brady et al. [19]	41% +		8% +
Wiklund et al. [8]	30%		5%
Laskin et al. [28]	37%		
Davidson et al. [22]	14%		20%

+ calculated from entire study sample and not restricted to RIS located in the appendicular skeleton, pelvis or trunk.

5. Discussion

RISs represent an important long-term complication of radiation therapy and patients display worse outcomes than those with de novo STS when compared with historical controls. In our study, we found that RIS occurred most commonly in the trunk usually more than a decade after irradiation of the primary tumor. The most common histologic subtype was UPS (42.2%). Mainstay treatment consisted of surgical resection, with less than one third of patients receiving RT or QT. At five years, less than half of the patients (45%) were alive and 39% and 27% developed local recurrence and metastasis, respectively. To the best of our knowledge, this study represents the first systematic review performed to assess the oncologic outcomes of RIS located in the extremities or trunk.

Our study has several limitations. First, due to the rarity of this entity, we included studies with a small number of patients. Moreover, some of the included studies combined data of radiation-induced STSs and bone sarcomas or included locations other than the trunk and limbs in the analysis. Additional cases may have been missed in cohorts that focused on soft tissue sarcomas but did not make the distinction between de novo STS and RIS. Second, additional variables such as the type of primary tumor, chemotherapy regimen, radiotherapy scheme, disease-specific survival, time to local recurrence and time to metastasis were not available in the majority of included studies. Although this limitation is inherent to most systematic reviews, it did limit the depth of our analysis. Third, publication bias may have been present, with studies reporting poorer oncologic outcomes being less likely to be published. Fourth, our analysis was restricted to RIS and did not compare outcomes with a controlled cohort of patients with de novo STS due to the nature of the published literature. This might limit the generalizability of our findings.

In our study, the mean patient age at the time of ST-RIS diagnosis was 58.4 years, and 54% of patients were women. A female predominance in RIS has been previously described and is attributed to the higher incidence of breast cancer, usually treated with RT, in this population [8,20]. The mean latency time that we found was 14.1 years. It is hypothesized that latency period may be linked to both radiation dose and type of sarcoma [26]. Wiklund et al. stated that there is an inverse relationship between radiation dose and latency time, implying a threshold dose for developing RIS [8]. Conversely, other authors have suggested that higher dosages of RT might result in longer latency period times. This is based on the idea that the malignant transformation of cells is directly proportional to RT dosage up to a certain point, after which RT reduces the number of at-risk cells. Thus, the risk of RIS reaches a peak and then decreases as the dosage keeps increasing [22,29].

The most common histological type of RIS was UPS. This is important as the histological STS subtype carries prognostic value in terms of overall and disease-specific survival [5]. Moreover, the link between histologic subtype and prognosis has also been demonstrated in RIS. Studies have reported that UPS and malignant peripheral nerve sheath tumor (MPNST) RIS have worse oncological outcomes compared to leiomyosarcoma, fibrosarcoma and myxofibrosarcoma [5]. In addition, there may be a link between latency time and histologic subtypes [5].

The optimal treatment strategy for RIS remains unknown, Due to its locations within a previously irradiated field, the therapeutic alternatives for RIS are more limited in comparison with de novo STS [4]. In our study, approximately two thirds (68%) of patients with RIS underwent surgery and 58% of them attained negative margins. Although wide resection is currently considered the cornerstone of RIS management, this procedure has a lower likelihood of resecting the tumor with negative margins compared to de novo STS [5,20]. A previous study by Callese et al. reported that R0 margins after the resection of an RIS ranged from 31 to 91% [20]. The ample variability in R0 margin rates can be explained by differences in patient selection for surgical management [20]. Moreover, soft tissue fibrosis caused by prior RT may further complicate the surgical approach, making tissue plane identification, the accurate determination of the tumor extent and surgical field exposure difficult [4]. In addition, soft tissue fibrosis can decrease the effects of chemotherapy [4]. In our study, only 29% of patients with RIS received chemotherapy,

lower than the rates reported in the literature for de novo STS. This pattern was not, however, seen in all studies included: Gladdy et al. reported that chemotherapy was used at a similar rate in both de novo STS and RIS [5]. It is important to highlight both the risks and benefits of chemotherapy, especially considering the large proportion of elderly patients and the fact that, historically, it has been mainly used for palliative care [26]. Novel discoveries and benefits in local control should incline physicians to use chemotherapy beyond palliative care and as a potentially useful tool for RIS management.

In our study, only 15% of patients received RT to treat the RIS, highlighting the reluctance of radiation oncologists to reirradiate these tumors. RT as a part of the management of RIS has been traditionally rejected due to concerns about increased toxicity and complications from tissue reirradiation [4]. Likewise, reirradiation can interfere with adequate margin resection, given that irradiated tissue has fibrotic changes that could be confused with tumoral tissue and vice versa. Riad et al. suggested that patients with locally RIS could benefit from reirradiation [4]. To consider reirradiation, adequate patient selection is critical and should consider the surgical margins, previous radiation dosage (Gy), volume of normal tissue irradiated, estimated normal tissue recovery after RT and presence of adjacent critical radiosensitive structures. Current RT technologies, such as image-guided radiotherapy (IMRT), brachytherapy or proton therapy, offer the ability to safeguard normal tissue while precisely targeting the affected area, providing greater flexibility in incorporating RT as a fundamental component of the management of RIS [4,20].

Outcomes in patients with RIS have been reported to be worse in comparison with sporadic STS [10,20,27]. In our study, the five-year overall survival was 45%, similar to what was found by Gladdy et al. (41%) and Kim et al. (45%) [5,27]. In contrast, Italiano et al. reported a higher five-year overall survival (51.9%). Their population, however, only included patients who received surgical management and obtained R0/R1 margins. Based on their results, they advocated for applying the same surgical curative treatment intent in RIS as in de novo sarcomas [10]. Even though the latest article reported a better outcome, still, when compared historically with de novo soft tissue sarcomas, the outcomes are inferior. The persistent poor overall survival in RIS, despite a recent slight increase reported by Italiano et al., can be attributed to the intrinsic histopathological characteristics of RISs, their limited response to adjuvant treatment and the higher rates of local recurrence and metastasis compared to de novo STS.

Our study found a metastasis rate of 28%, which is lower than the 50–70% rate for de novo high-grade STS [30–32]. In contrast, Callesen et al. reported a higher metastasis rate at the time of diagnosis in patients with RIS (22% compared to 10% for de novo STS) [20,32]. This difference can be attributed to the longer latency period and the more aggressive nature of the RIS tumor [20,26]. We also observed a local recurrence rate of 38%, lower than previously reported by other studies (ranging from 41 to 65%) [7,12,21], but higher than the 26% rate reported by Riad et al. [4]. It is worth noting that both our findings and those described in the literature of RIS are significantly higher than the local recurrence of 6.5 to 9% reported for de novo STS [4,33–35]. Notably, lower local recurrence rates have been observed in patients with RIS who underwent reirradiation (7.7%), compared to patients who only received surgical management (34.5%) [4].

6. Conclusions

Our study represents the first and largest systematic review performed to assess outcomes of patients with RIS. The optimal treatment strategy for this rare entity remains unknown, yet expanding treatment strategies beyond surgical resection is supported by more recent studies. In our study, the most common treatment was surgical resection, with RT and chemotherapy being administered in less than one third of patients. Patients with RIS exhibited poor oncologic outcomes, with the five-year overall survival below 50% and metastasis rate at 27%. Local recurrence was reported in 39% of patients. Future studies should evaluate the efficiency of combined treatment strategies on this very rare and unique group of patients. Moreover, studies should compare RIS with de novo STS

while controlling for confounders to have additional insight on the biologic behavior of these tumors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cancers15235584/s1, Supplementary Table S1: Additional information on included studies.

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Radiation-induced sarcomas: A single referral cancer center experience and literature review

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Background and objective: The oncogenic effect of ionizing radiation is widely known. Sarcomas developing after radiation therapy (RT), termed "iatrogenic disease of success", represent a growing problem, since the advancements in cancer management and screening programs have increased the number of long-term cancer survivors. Although many patients have been treated with radiation therapy, only few data are available on radiation-induced sarcomas (RIS).

Methods: We examined the medical and radiological records of 186 patients with histologically proven soft tissue and bone sarcomas, which referred to IRCCS CROB Centro di Riferimento Oncologico della Basilicata from January 2009 to May 2022. Among them, seven patients received a histological diagnosis of secondary RIS, according to Cahan's criteria. Clinicopathological features and treatment follow-up data of RIS patients were retrospectively analyzed.

Results: Among these secondary RIS, five arose in irradiated breast cancer (5/2,570, 0.19%) and two in irradiated head and neck cancer (2/1,986, 0.10%) patients, with a mean onset latency time of 7.3 years. The histology of RIS was one desmoid tumor, two angiosarcomas, one chondrosarcoma, two leiomyosarcomas, and one undifferentiated pleomorphic sarcoma. Out of the seven RIS, one received radiotherapy, one received electrochemotherapy (ECT), one received a second-line chemotherapy, three were subjected to three lines of chemotherapy, and one underwent radiofrequency ablation, chemotherapy, and ECT. Median survival time is 36 months. No significant survival differences were found stratifying patients for age at RT, latency time, and age at RIS diagnosis.

Conclusions: RIS represents a possible complication for long-survivor cancer patients. Therefore, adherence to a strict follow-up after the radiation treatment is recommended to allow early diagnosis and optimal management of RIS patients. After the planned follow-up period, considering the long-term risk to develop a RIS, a specific multispecialty survivorship care plan could be of benefit for patients.

KEYWORDS

breast cancer, head and neck cancer, radiation-induced sarcoma, radiotherapy, long-term radiation effects

Introduction

Radiation therapy (RT) represents the main treatment strategy for more than half of cancer patients (1–3), since it entails improvement of the survival rates and long-term overall survival in many types of cancer. Therefore, the employment of this treatment option is growing. Indeed, as an example, a Korean study reported a 65% increase in cancer patients who underwent RT from 2006 to 2013 (4). Despite these undoubted benefits, RT is found to be associated with the onset of a rare iatrogenic malignancy, known as "radiation-induced sarcoma" (RIS), which represents about 3% of all soft tissue sarcomas (5). This adverse event is characterized by poor 5-year overall survival, ranging from 10% to 36% in relation to disease stage at diagnosis (1). Therefore, RIS is considered an arduous challenge for physicians. It also represents a growing clinical problem, likely associated with the increasing number of long-term cancer survivors determined by the advancements in cancer screening programs and patient management (6, 7).

The first cases of sarcoma following RT were observed in 1922 by Beck and Marsch in patients irradiated to treat tuberculous bone disease (8, 9). Subsequently, in 1936, Warren and Sommer described complications after irradiation of breast carcinoma in 81 patients (9). In 1948, based on 11 cases of post-radiation osteosarcoma (PRS), Cahan and Woodard defined the following criteria for RIS diagnosis (10):

a) No evidence of the new tumor at RT time;
b) Sarcoma arises in the irradiated field;
c) Relatively long latency period before sarcoma onset; and
d) Histologically proven sarcoma.

A large analysis of the Surveillance, Epidemiology, and End Results (SEER) registries found a 257% increased risk of secondary bone sarcoma in patients who received radiotherapy compared to the general population (11). Recently, these data were examined by Snow et al., who reported that, after cervical cancer, breast cancer has the highest risk of RIS (88.2% and 78.3%, respectively) (12). RIS after breast cancer RT shows a wide range of histopathologic subtypes, among which malignant fibrous histiocytoma is the most common. Less frequent findings include leiomyosarcoma, liposarcoma, fibrosarcoma, and angiosarcoma, and rarely chondrosarcoma and osteosarcoma. These secondary RIS are usually high-grade tumors variable in size, whose histological features include presence of spindle-shaped tumor cells, hemorrhagic tumor nodules, abundant mitotic figures, and necrosis (13).

RIS of the head and neck also represents a relevant problem since, although rare, they are a lethal consequence of RT. Its average frequency was about 0.15% with a mean latency period, the interval between RT on the primary lesion and the onset of secondary sarcoma, of about 11 years. Histologically, RIS of the head and neck are mainly ascribable to osteosarcoma and fibrosarcoma (14).

Here, we performed a retrospective study on patients' records to investigate the clinical and pathological features of RIS cases that accessed IRCCS CROB Centro di Riferimento Oncologico della Basilicata from 2009 to 2022.

Materials and methods

Patient cohort and data collection

We examined the medical record of all histologically diagnosed sarcoma in patients managed from 2009 to 2022, included in both the Basilicata Cancer Registry and the Institutional Electronic Health Dossier. The latter also comprises patients from nearby regions. All data were retrieved from patients who gave their informed consent at the first access or afterwards on request.

Overall, there were 186 cases (85 male and 101 female patients) of sarcomas with a mean age of 59.7 years (range: 15–91 years). At the time of writing (June 2022), patients are followed up in an outpatient setting. The mean time of follow-up

is 58.5 months (range: 0.6–380.7 months). Their geographical origin is mainly Basilicata (121), Campania (38), and Puglia (16) (Table 1).

Diagnosis and treatments

The first diagnosis was made at CROB for 116 patients. Seventy-two patients underwent radical surgical excision. Metastases were detected in 74 patients through total body computed tomography (CT) examination at first diagnosis, whereas in 73 cases, new metastatic lesions appeared during follow-up. All patients were treated at our center, except one osteosarcoma patient who was managed at Rizzoli Orthopedic Hospital in Bologna. Several treatment regimens were administered as summarized in Table 1. Ninety patients received chemotherapy, 33 of whom received only the first-line setting, 50 patients also received a second-line treatment schedule, and 29 patients received three chemotherapy lines. Notably, off-label and/or targeted therapy regimens were tried. One patient diagnosed with carcinosarcoma (MMMT) received FOLFIRI regimen. In three cases, olaratumab was the first-line treatment. One patient with a myofibroblastic inflammatory tumor of sclera-conjunctiva, positive for anaplastic lymphoma

TABLE 1 General characteristics and management information of the enrolled sarcoma patients.

Sarcoma patients (from 2009 to 2022)	***N* = 186**
On follow-up	52
Sex (M/F)	85/101
Age, mean (range)	59.7 (15–91)
Patient territorial distribution	
• **Basilicata**	121
• **Puglia**	16
• **Campania**	38
• **Other**	11
Center of diagnosis/surgery	
• **IRCCS CROB**	116
• **Other**	70
Metastasis at diagnosis (Yes/No)	74/112
Disease progression	73
Surgical excision	72
Chemotherapy	90
• **Neoadjuvant**	7
• **1st line**	83 (33 patients only one line)
• **2nd line**	50 (I+II)
• **3rd line**	29 (I+II+III)
• **4th line**	15 (I+II+III+IV)
• **5th line**	9 (I+II+II+IV+V)
• **6th line**	3 (I+II+II+IV+V+VI)
Eribulina	2
Olaratumab	3
Crizotinib	1
Imatinib (Cordoma)	1
FOLFIRI/FUFA (carcinosarcoma-MMMT)	1
Pomalidomide (Kaposi sarcoma)	1
Protocol ISG/SSG (Ewing sarcoma)	1
Proton therapy	1
Autologous transplant	1
Brachytherapy	2
Electrochemotherapy	13
Radiotherapy	40
Palliative	6
Adjuvant	34
Months of follow-up, mean (range)	58.5 (0.6–380.7)

kinase mutation (ALK+), was treated with crizotinib. One patient received imatinib to treat cordoma.

Among the 186 patients, 40 patients received external radiotherapy, 2 cases received brachytherapy, and for 13 patients, electrochemotherapy was employed as local therapy.

Selection criteria of radiation-induced sarcoma

Criteria by Cahan et al. were used to identify RIS patients (10). For further evaluations, detailed epidemiological, clinical, pathological, and treatment history and survival information were collected.

Statistical analysis

The association of patients' overall survival with age at RT, at RIS, or latency time was estimated by log-rank test, after categorization of time in classes and using the *survminer* R package (15). In a similar way, association between RIS risk and age at RT, based on latency time, was explored. Survival curves were then plotted using the Kaplan–Meier method. Hazard ratios were also estimated for each variable by Cox proportional hazards regression model included in the *survival* package (16).

Results

Among 186 sarcoma patients, we identified seven (3.8%) cases fulfilling Cahan's criteria. In particular, five RIS arose in the irradiated field of breast cancer patients and two in that of head and neck cancer patients. To better define RIS incidence, we retrospectively analyzed all breast and head and neck primary tumors that underwent radiation therapy. Overall, we found 0.15% (7/4,556) of RIS incidence, in which breast cancer accounts for 0.19% (5/2,570), whereas head and neck cancer accounts for 0.10% (2/1,986). Histological evaluation of RIS found one desmoid tumor, two angiosarcomas, one chondrosarcoma, two leiomyosarcomas, and one undifferentiated pleomorphic sarcoma (Table 2). Out of the seven RIS patients, one received radiotherapy, one was treated with electrochemotherapy (ECT), one received a second-line chemotherapy, three underwent three lines of chemotherapy, and one was treated with radiofrequency ablation, chemotherapy, and ECT.

Mean latency time was 7.3 years, ranging from 2 to 14 years. The overall median survival is 36 months (Figure 1A). No significant survival differences, likely due to the limited number of RIS cases, were found by stratifying patients for age at RT (36 *vs.* 28 months, ≤60 *vs.* >60 years), latency time (32 *vs.* 45 months, ≤7 *vs.* >7 years), and age at RIS occurrence (32.0 *vs.* 30.5 months, ≤67 *vs.* >67 years) (Figures 1B–D). Cox hazard ratio analysis also did not show any association with these variables (Figure 1E). Similarly, RIS risk and latency time are not associated with age at RT (7 *vs.* 8 years, ≤60 *vs.* >60 years, respectively) (Figure 1F). A detailed case presentation of clinical and pathological findings, including treatments administered and outcomes, is reported below.

Case 1

A 40-year-old man, in July 2014, had a diagnosis of primary epidermoid carcinoma in the right vocal cord and left lung, stage pT4aN2cM0 and grade G3. In January 2015, both masses were radically excised after neoadjuvant radiotherapy with 66 Gy in 33 fractions on intensity-modulated radiation therapy (IMRT) mode. The patient was free of disease for 15 months until, in March 2016, he received a diagnosis of desmoid tumor in the nuchal area, external to the hot spot of the previously irradiated field. Histological evaluation on a core biopsy described a group of spindle cells included in a collagen matrix arranged as parallel fibers; less than 1/10 HPF (high-power field) mitoses were detected, leading to a diagnosis of extra-abdominal fibromatosis-desmoid tumor. Immunohistochemical staining highlighted cells positive for desmine, SMA (smooth muscle actin), negative for S100, and a Ki67 index of 4%. Angio- and neural invasion was also depicted. After case evaluation by the Institutional Multidisciplinary Tumor Board and its discussion with experts from a rare tumor Comprehensive Cancer Center, the case was considered unsuitable for surgical excision due to the presence of a locally advanced disease infiltrating vascular and nervous structures. The patient was asymptomatic and, considering the poor chemosensitivity of desmoid tumors, he entered on a follow-up care program. In April 2018, due to lesion size increase and localized pain, the patient started a chemotherapy regimen with a combination of two oral drugs, vinorelbine and methotrexate, for 15 weekly cycles. After four months of treatment, due to clinical and radiological disease progression (DP), the patient was treated with second-line chemotherapy consisting of six cycles of a 3-week doxorubicin and dacarbazine regimen. In January 2019, at disease status assessment, the patient had a partial response (PR) and then was addressed to follow-up (every 3 months for the first 2 years, and then every 6 months). At the last follow-up (September 2021), according to RECIST criteria, a further reduction of tumor size was noticed.

Case 2

The patient is a 46-year-old woman diagnosed in 2006 with nasopharyngeal carcinoma. She was treated with radiotherapy

TABLE 2 Histological features, therapeutic management, and follow-up information of radiation-induced sarcomas.

PN	Gender	Primary cancer TNM	Radiotherapy mode/dose	CCRT	Age at RT	Age at RIS	Latency (years)	Location of RIS	Pathology subtypes	Treatment of RIS	Resection Result	Outcome
1	M	pT4aN2cM0	IMRT/66 Gy	Y	40	42	2	Nuchal region	Desmoid tumor	CHT	N/A	AWD 08.09.2021 67 months
2	F	T2bN3	3D CRT/ 70 Gy	Y	46	53	7	Left sternocleidomastoid muscle	Leiomyosarcoma + pleomorphic areas	S + CHT	R0	DOD 23.08.2016 36 months
3	F	pT1N1(10/19) pT1N0	3D CRT photons/ 50 + 10 Gy	Y	63	75	12	Left breast	Chondrosarcoma	S + CHT	R0	DOD 28.09.2018 45 months
4	F	pT1cN0	3D CRT photons/ 50 Gy 3D CRT electrons 9 MeV/10 Gy	Y	75	77	2	Left scapulo-humeral	Leiomyosarcoma + undifferentiated high grade pleomorphic sarcoma	RT	R1	DOD 04.01.2014 16 months
5	F	pT1cN0	3D CRT photons/ 50 + 10 Gy	Y	61	67	6	Left breast	High grade angiosarcoma	ECT	N/A	DOD 29.10.2019 28 months
6	F	pT2N1(8/24)	3D CRT photons/ 50 + 10 Gy	Y	53	67	14	Left armpit + left thoracic wall	High-grade undifferentiated pleomorphic sarcoma (myofibroblastic sarcoma)	CHT	N/A	DOD 15.02.2021 5 months
7	F	pT1N1(1/18)	3D CRT photons/ 50 +10 Gy	Y	63	73	10	Left breast	High-grade angiosarcoma	Radiofrequency ablation + CHT + ECT	R0	AWD Last FU 01.03.2022 14 months

TNM stage according to the American Joint Committee of Cancer (AJCC) staging system (7th edition). PN, Patient number; M, Male; F, Female; CCRT, Concurrent Chemoradiotherapy; S + CHT, Surgery + Chemotherapy; RT, Radiotherapy, CHT, Chemotherapy; ECT, Electrochemotherapy; IMRT, Intensity-modulated radiotherapy; 3D CRT, three-dimensional conformal radiation therapy; DOD, Dead of disease; AWD, Alive with disease; N/A, not applicable.

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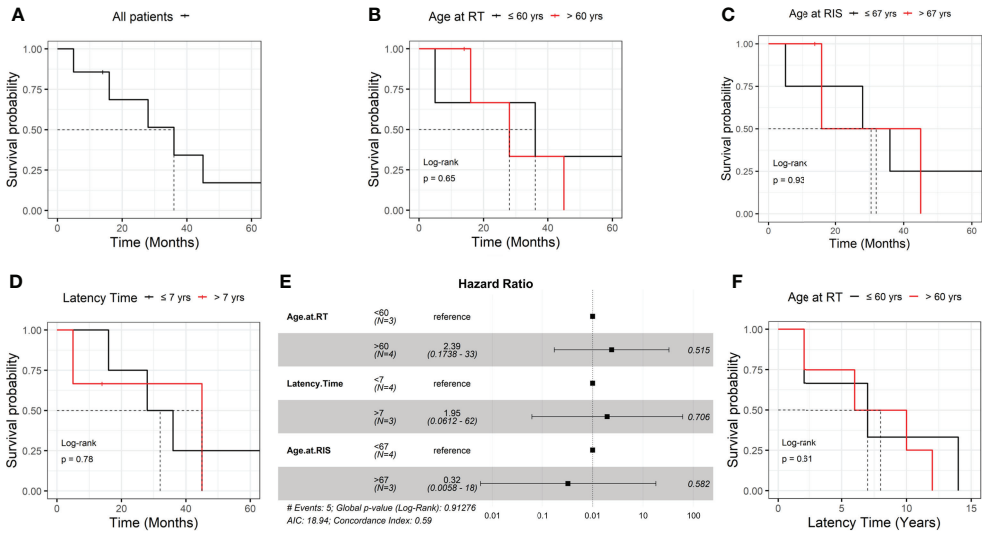

FIGURE 1
Association of radiation-induced sarcoma patients' overall survival with different parameters **(A–E)**. Association of radiation-induced sarcoma onset and age at radiation therapy **(F)**. RT, radiation therapy; RIS, radiation-induced sarcoma.

(70 Gy in 35 fractions) combined with weekly cisplatin infusions (five of six cycles regularly administered; the last cycle was suspended due to a suspect of cisplatin-induced grade 4 pancytopenia). The patient's clinical history included essential hypertension, hysterectomy for fibromyomas (in 1997), and family history of cancer (a 50-year-old brother with stage III colon cancer). A bilateral hypoacusis as a consequence of radiotherapy was recorded.

After 7 years (September 2013), during routine follow-up, clinical and radiological diagnosis of a mass on the left side of the neck (sternocleidomastoid muscle), referred to as RIS, was made. The patient underwent radical surgery of the left sternocleidomastoid muscle. Histology showed a high-grade mesenchymal neoplasia, consisting of atypical cellular elements, partly fused, with moderate-severe atypia and myogenic differentiation, partly round and oval, sometimes pleomorphic, arranged mostly in bundles and fascicles. Numerous mitotic figures and necrosis areas were observed (Grade 3). Immunohistochemical characterization showed positivity for vimentin, CD34, SMA, and negativity for CD30, CD68, CD31, desmin, and S100. Ki67 index was equal to 70%. Six months later, a local relapse was excised from the left anterior chest wall. After further 6 months, in December 2014, computed tomography (CT) scan showed multiple bilateral lung metastases and the patient received six cycles of first-line chemotherapy based on the combination of gemcitabine and docetaxel. During disease evaluation in April 2015, a strong DP with sternal relapse and pulmonary metastases accompanied by stable lymph nodes was noticed.

Starting from May 2015, six cycles of high-dose ifosfamide continuous infusion were administered as second-line chemotherapy. A minimal partial regression of disease was recorded under CT scan in January 2016. Three months later, an additional CT scan showed lung metastases progression, and dacarbazine, as third-line chemotherapy, was administered for three cycles. In August 2016, the patient was referred to the emergency room for stroke and she died. No necropsy was made and pulmonary embolism was assumed as the causal event.

Case 3

The case is a 63-year-old woman with a history of hormone-sensitive bilateral breast cancer (stage II) treated with a bilateral quadrantectomy and axillary lymph node dissection. The patient reported a family history of cancer, a brother and sister with gastric cancer, and a nephew with breast neoplasm.

The patient received a combination of adjuvant radiotherapy (50 Gy by photons in 25 fractions + 10 Gy by two 6-MeV tangential electrons beams in 5 fractions) and chemotherapy (epirubicin plus paclitaxel for four cycles and cyclophosphamide plus methotrexate plus fluorouracil for four cycles), hormone therapy with tamoxifen for 1 year, and anastrozole for 5 years to avoid endometrial hyperplasia.

After 11 years of follow-up, clinical examination of breast documented a mass in the residual of excised left breast and the patient was then subjected to left radical mastectomy. Histologically, it was referred to as poorly differentiated (G3)

metaplastic carcinoma of the breast with mesenchymal differentiation (MCMD), score 8 according to Elston and Ellis criteria. Areas of high-grade chondrosarcoma, which constitute 30% of the neoplasm, were present. Immunohistochemical characterization revealed positivity for Vimentin and S100, whereas tissue sections were negative for cytokeratin AE1/AE3 and 34beta E12, and p63. Tissue specimens were also estrogen receptor (ER) and progesterone receptor (PR) negative, and slightly positive for HER2. Ki67^{+} cells were 20%. No vascular and neural invasion were observed. TNM staging was rpT2pNx. After surgery, the patient entered a clinical and radiological follow-up program, as she refused adjuvant therapy. Nine months later, a follow-up chest x-ray showed multiple secondary lung lesions unsuitable for surgical excision. After a multispecialty evaluation, based on the absence of symptoms and the palliative intent of treatment, the patient underwent 3 days of ifosfamide continuous infusion; cycles were repeated every 3 weeks. After six cycles, the patient had partial response and she was asymptomatic during the subsequent follow-up period. Thirteen months later, a CT scan showed lung disease progression that required a systemic therapy consisting of 1,000 mg/mq gemcitabine on days 1 and 8, every 3 weeks. The patient did not improve after four cycles of treatment (June 2017). Since then, the patient chose a 1-month rest period from chemotherapy, until a further progression of lung lesions was documented. A third-line chemotherapy regimen, based on continuous infusion of high-dose ifosfamide, was administered for seven consecutive days over 14 days for eight cycles. In July 2018, pulmonary disease further progressed and, after 2 months, the patient died due to respiratory failure.

Case 4

A 75-year-old woman underwent right quadrantectomy surgery for a pT1cN0, estrogen receptor positive breast cancer. The patient was treated with CMF (cyclophosphamide plus methotrexate plus 5-fluorouracil) in an adjuvant chemotherapy setting and RT of the right breast (50 Gy by photons in 25 fractions + 10 Gy by single direct 9-MeV electron field in 5 fractions), followed by 5 years of anastrozole therapy. Two years later, during a follow-up visit, a left parascapular mass was noticed. Biopsy and radical excision showed moderately differentiated leiomyosarcoma (G2) showing giant cells with morphologically recognizable smooth muscle differentiation, histological grade 6 according to the French Federation of Cancer Centers Sarcoma Group, and pT2a according to TNM staging (7th ed.). Histologically, it was described as a malignant mesenchymal neoplasm composed of spindle cells with a marked cyto-nuclear atypia and eosinophilic poorly defined cytoplasm, organized in parallel bundles. The immunophenotypic profile was as follows: positive for vimentin, SMA, EMA (epithelial membrane antigen), and actin (clone HHF-35), and negative for CK-pan, Melan A, desmin, CD34, and S-100. The patient underwent post-surgery radiotherapy with 200 cGy for 30 fractions. After 14 months of follow-up, a local relapse in the left humerus-scapular region was observed and excised. Histological evaluation defined a high-grade pleomorphic sarcoma with skin ulcerative lesions, infiltrating subcutaneous tissue and showing vascular embolization. Due to the patient's poor general condition and comorbidities, she was not suitable for further systemic chemotherapy, and, after a period of palliative care, she died.

Case 5

The patient is a 61-year-old woman with a diagnosis of left breast infiltrating ductal carcinoma, pT1cN0, grade G2, ER 98%, PGR 20%, HER2+, who underwent quadrantectomy and axillary lymph node dissection followed by adjuvant chemotherapy, radiotherapy (50 Gy in 25 fractions + 10 Gy in 5 fractions by photons), and letrozole administration for 5 years. After 6 years of follow-up, the patient was diagnosed with a left breast locally advanced angiosarcoma, for which she received neo-adjuvant chemotherapy. One year later, the patient underwent a left mastectomy. After one month, a new mass was noticed. Nine months onward, the patient had right breast mammography and bilateral ultrasound examination, which showed a new lesion on the right breast along with an ulceration on the left thoracic wall. The patient met with our plastic surgery team and she was then subjected to surgical excision and electrochemotherapy for both lesions. Histological examination documented a high-grade angiosarcoma (G3), positive for Factor VIII and CD31, with extensive areas of necrosis and ulceration. During the last follow-up record, 3 months after surgery, she showed local condition improvement but soon after she died.

Case 6

The patient is a 53-year-old woman with a left breast triple-negative infiltrating ductal carcinoma, pT2N1 (N+8/24), G3, surgically excised through left radical mastectomy and axillary lymph node dissection. Following the decision of the Multispecialty Tumor Board, adjuvant antracycline–paclitaxel combination regimen was administered. After 12 years, a local relapse (grade 3 invasive adenocarcinoma) infiltrating dermis and muscle tissue and extending to the thoracic wall was diagnosed. The pathologist described a triple-negative breast cancer with Ki67 index at 50%. The patient underwent surgical excision of pectoral muscle and further chemotherapy treatment with CMF was administered. Seven months onward, radicalization surgery was performed. The patient was then subjected to chemotherapy with epirubicin and paclitaxel, and local radiotherapy plus CWB (chest wall boost) (50 Gy in 25 fractions + 10 Gy in 5 fractions by photons).

The patient had regular clinical and radiological follow-up for 14 years until a left axillar mass and enlarged lymph nodes

were detected. Biopsies of the left chest wall showed neoplasm from globose cells with highly pleomorphic nuclei immersed in large necrosis areas. The immunophenotypic profile was found to be positive for CD10, desmin, muscle actin HHF-35, and CD68 (occasionally), and negative for Myo D1, SMA, S-100, CK-pan, CD31, CD34, and Factor VIII; Ki67 proliferation index was 50%. On these bases, it was referred to as a high-grade phyllodes tumor or sarcoma with myofibroblastic/pleomorphic differentiation. Disease evaluation with magnetic resonance imaging (MRI) and CT showed an extensive mass with lymph node metastases. The patient received chemotherapy based on epirubicin and ifosfamide. After two cycles, the patient's conditions deteriorated with massive pleural effusion and chest invasion, which led to the patient's death.

Case 7

The case concerns a 63-year-old woman who, in 2011, underwent left breast quadrantectomy and axillary lymph node dissection for infiltrating ductal breast cancer [pT1cN1 (1/18), G2, ER: 90%, PGR: 60%, Ki67 index at 15%, and HER2 negative]. Thereafter, the patient received chemotherapy with six cycles of FEC regimen (5-fluorouracil, epidoxorubicin, and cyclophosphamide), radiotherapy (50 Gy in 25 fractions + 10 Gy in 5 fractions by photons), and letrozole for 5 years. During the follow-up, 9 years later, there was evidence of an ulcerated and bleeding left breast lump, 7 cm in diameter, adherent to the chest wall, and a suspect of bilateral secondary pulmonary lesions through total body CT. A biopsy of the lesion documented a morphological picture showing fibrotic tissue and atypical epithelioid cell aggregates that sometimes optically border empty spaces. The absence of Pan-cytokeratin and positivity for vascular markers was reported. Ki67 was positive in 60% of neoplastic cells. The overall picture was traceable to angiosarcoma. The patient received a single radiofrequency thermoablation session on the breast lesion, resulting in suspension of bleeding, and a first-line chemotherapy for radio-induced angiosarcoma based on three cycles of gemcitabine and docetaxel but without benefit. In July 2021, after internal collegial discussion and sharing the case with a Cancer Center specialized in sarcomas, the patient received one electrochemotherapy session and then a second-line chemotherapy based on weekly doxorubicin administration. A new disease evaluation was made after nine chemotherapy cycles; CT images showed stable pulmonary nodes and no new mass onset. The patient was subjected to another session of electrochemotherapy after 6 months. Biopsy showed chronic and acute inflammation with ascending characters and giant cells from foreign body, marked fibrosis, and epidermal atrophy but no evidence of neoplasm. The patient received 15 cycles of chemotherapy. During the last follow up, in March 2022, she has shown stable disease.

Discussion

Although radiotherapy represents one of the cornerstones in cancer treatment, it has been assessed that RIS could be a complication. Since the interval between the RT and RIS occurrence is long, it is a key point to perform a strict and continuous follow-up to make an early and accurate diagnosis in order to guarantee an adequate treatment. Overall, RIS represented less than 4% of all sarcoma patients, and arose in 0.19% and 0.10% of RT-treated breast and head and neck cancers, respectively. These results are in line with previous reports (5, 12, 17–20). Our cohort of patients showed clinicopathological features similar to those in existing literature (13, 14). In our study, female patients with RIS were about 85% (6/7), according to the high prevalence of primary breast cancer in women (21). In previous studies, a median age of primary tumor diagnosis ranging from 41 to 46 years, a median latency period to RIS from 8 to 14 years, and a median age at RIS presentation ranging from 52 to 59 years have been reported (21). In slight contrast, we found that our patients were older at primary cancer diagnosis (57.3 years) and that they were characterized by a shorter RIS latency period (7.6 years), which also delayed the median age at RIS diagnosis (64.8 years) (14). This shorter latency time might be in part associated with concurrent chemotherapy administered to treat primary tumor, as previously described by Zhang et al. (22). However, the median survival time, 36 months, was found to be quite comparable to that from other reports (14, 23).

Despite their low incidence, RIS is characterized by high aggressiveness from both local and systemic points of view, which results in high mortality rates. Recent reports highlighted the non-inferiority of the hypofractionated radiation regimen as compared with the conventional one (24, 25). Notably, although long-term real-life data on the RIS risk associated with hypofractionated irradiation are lacking, some reports highlight the possible occurrence of secondary cancers in the irradiated field (26, 27). R0 resection is widely considered the only curative chance for these patients (28), although all RIS patients in our case series had tumor relapse after surgical resection. Moreover, our patients received scarce benefits from multiple lines of chemotherapy. However, the poor prognosis of RIS patients did not discourage the employment of radiotherapy, an indispensable therapeutic approach for cancer treatment, since its benefits undoubtedly outweigh the risks.

Conclusions

RIS is a possible complication of long-survivor cancer patients; thus, much attention has to be paid to early diagnose these cancers to employ optimal lifesaving therapies. Adherence to a strict follow-up regimen after the radiation treatment to assess and mitigate the risk of post-radiation tumor onset is recommended. After the

planned follow-up period, considering the long-term risk to develop a RIS, it is also necessary to apply a specific survivorship care plan. Our center is working to organize a multispecialty survivorship program that will include hospital physicians, general practitioners, and outsource experts specialized in supportive discipline, including nutritional support.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SR and AMB designed the work. LCO, SL, AB, APS collected data. SL, FA, and SR analysed data. GM and AMB interpreted data. LCO, SL, and SR drafted the work. AS, GF, and AMB substantially revised the work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Radiation-induced Sarcoma

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Opinion statement

Radiation-induced sarcomas can originate in either the irradiated bone or soft tissues. Most of these tumors are high-grade. The most common histologic subtypes are malignant fibrous histiocytoma (MFH) and osteosarcoma, although other histologies (*eg*, angiosarcoma, rhabdomyosarcoma) can occur. Tumor size and grade are the two most important prognostic factors for soft tissue sarcomas, including those associated with radiation therapy. The therapy is therefore dictated by the risk of distant metastases. High-grade tumors that are larger than 5 cm should be treated with primary chemotherapy followed by a margin-negative surgical excision of the residual disease. All low-grade tumors and high-grade tumors 5 cm or smaller should be treated with a margin-negative surgical excision, and systemic chemotherapy should be considered when a negative margin is difficult or impossible to accomplish. Radiation-induced sarcomas (either MFH or osteosarcoma) originating in bone should be approached with primary chemotherapy followed by a margin-negative excision similar to de novo bone sarcomas. The dose-intensity of the active agents should be adjusted appropriately for the age, performance status, and prior therapy in a given patient.

Introduction

The term radiation-induced sarcoma implies that radiation is the sole etiologic factor, which, although true in most cases, may underscore the contributory effects of other carcinogenic agents like alkylating agent chemotherapy or other yet unknown or not well-characterized factors. Some authors therefore prefer the term radiation-associated or postirradiation sarcomas. Recent advances in molecular techniques have helped improve our understanding of the pathogenesis of this entity. The double-strand DNA damage induced by ionizing radiation is thought to cause genomic instability that could be the etiologic factor for resultant malignancies. The genetic changes in radiation-induced sarcomas, however, are not well characterized. Nakanishi *et al.* [1] analyzed p53 gene mutations by polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) on paraffin-embedded tumor specimens from 24 patients with postradiation sarcomas. Direct sequencing of the SSCP product revealed a total of 58 mutations in 21 of 24 cases (88%) compared with the 20% frequency of p53 mutations in sporadic soft-tissue sarcomas, suggesting that radiation may be inducing sarcoma development via p53 gene mutations [1]. From a clinical standpoint, the first association between exposure to therapeutic radiation and occurrence of a sarcoma was recognized in 1922 by Beck, who reported the development of bone sarcomas in patients who had received radiation therapy for tuberculous arthritis [2]. A few years later, in 1929, Martland and Humphries [3] described the association of osteosarcoma in watch dial painters who ingested radium while using it as a luminous paint. It took another couple of decades, however, for postradiation bone sarcoma to be an established entity—small series of patients, who were irradiated for benign diseases such as giant-cell tumors and aneurysmal bone cysts, developed sarcomas within the bone [4,5]. Cahan *et al.* [4] were the first ones to establish criteria for the diagnosis of a postradiation sarcoma, which included the development of a sarcoma within the path of the radiation beam, with at least a 5-year latency period between the radiation therapy and the diagnosis of a histologically confirmed sarcoma. These criteria were later modified by Arlen *et al.* [6] to include the tissues adjacent to the path of the radiation beam also at risk for the development of a sarcoma, and a latency period of at least 3 to 4 years as opposed to 5 years.

The clinical features of postradiation sarcomas have been well defined by two contemporary reviews of large series of patients. One is a literature review of 344 patients [7] and the other is a single institution experience with 160 patients over a 46-year period. [8•]. The earlier literature characterizes postradiation bone sarcomas much better than its soft-tissue counterparts because of its higher frequency during the orthovoltage radiation therapy era, which is absorbed more quickly by bone than by soft tissues. In the modern era of megavoltage radiation therapy, the occurrence of postradiation sarcomas has not been eliminated, suggesting that the energy source of radiation is irrelevant. The best estimates of the incidence of postradiation sarcomas ranges between 0.03% (of patients who receive radiation) to 0.2% (of patients who have received radiation and survived 5 years). The incidence does increase with time, as is noted in long-term survivors of childhood malignancies (*eg*, retinoblastoma). Postradiation sarcomas are more common in females because of breast and cervical cancers, which are often treated with radiation therapy and have a prolonged survival. Lymphoma, especially Hodgkin's disease and retinoblastoma, is the other primary malignancy treated frequently with radiation and associated with long-term survival that precedes a postradiation sarcoma. The median latency period is approximately 10 years, ranging from 2 to 3 years to up to 50 years. The longest interval has been reported in patients treated with brachytherapy +/- external beam radiation therapy, and the shortest interval was seen in patients treated with supervoltage therapy [7]. A wide range of doses of radiation (8 to more than 60 Gy) has been reported to result in a postradiation sarcoma. The majority of cases have had therapeutic doses of radiation with a median of about 50 Gy. In a review of second malignancies after Ewing's sarcoma, Kuttesch *et al.* found no secondary sarcomas in patients receiving less than 48 Gy compared with an absolute risk of 130 cases per 10,000 person-years of observation among patients who had received 60 Gy or more, suggesting dose dependence [9]. The median age of the patients is in the fifth decade of life. There are, however, two peaks: one in the second decade and the other one in the over 50 age group. The first peak mainly occurs in patients with retinoblastoma, and the second peak includes the adult solid tumors outlined above. The chest wall and the pelvis are the two most common sites, again based on the antecedent malignancies. In the Memorial Sloan Kettering Cancer Center (MSKCC) series, angiosarcoma was the most common histology in the chest and osteosarcoma, and malignant fibrous histiocytoma (MFH) comprised the majority of the tumors at the other sites [8•]. Limited data are available on the grade of these tumors in the literature; however, in the Memorial Sloan-Kettering Cancer Center (MSKCC) series, 87% of the tumors were high grade. Most patients present with a locally advanced tumor that is typically greater than 5 cm in size and deep to the investing fascia. A multivariate analysis of various prognostic factors was performed in the MSKCC series, and independent variables included the presence of metastatic disease, completeness of operative resection, and size of the primary tumors. Grade is also a very likely prognostic factor; however, the paucity of low-grade tumors in this category limits its comparison to high-grade tumors. In the MSKCC series, survival was independent of the site of disease, bone versus soft tissue origin, histology, and latency period.

Treatment

- In their literature review of 344 cases reported prior to 1987, Robinson *et al.* [7] found that 46% were reported to be operable, 28% were advanced stage patients, and no treatment-related information was available in the remaining 27% of patients. A total of 70 patients (20%) had received chemotherapy and, interestingly, 67 patients received additional radiation therapy. Thirty-four patients were reported to have a complete response, and 17 patients had a partial response to chemotherapy or radiation therapy. The median survival of the 266 patients with available information was 12 months. Two-year survival was 22%, and 5-year survival was 11% [7]. In the MSKCC series spanning between 1943 and 1989, 148 of 160 patients had localized disease, and 12 had metastatic disease at presentation. Seventy-five patients underwent complete resection, 32 underwent incomplete resection, 33 with advanced disease had no surgery, and no clear information was available on the remaining 20 patients. Thirty-two patients received adjuvant doxorubicin-based chemotherapy, and there was no difference in their 5-year survival compared with the group who did not receive chemotherapy (45% vs 44%, $P = 0.72$) [8•].

- Tabone *et al.* [10••] performed a review of the outcome of patients with postradiation osteosarcoma in the modern chemotherapy era between 1981 and 1996. Of 23 patients with osteosarcoma, nine had an extremity primary, seven had a girdle bone primary, six had craniofacial primary, and one had a first cervical vertebra primary. Fifteen patients had complete resection, and 14 patients received intensive chemotherapy before or after surgery. At a median follow-up of 7.5 years, the event-free survival was 41% and overall survival was 50%.

Chemotherapy

Postradiation bone sarcomas

Most of these tumors are high grade and histologically resemble either an osteosarcoma or an MFH. These tumors are sensitive to standard bone sarcoma chemotherapy, namely doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate. The recommended approach for this subset of patients is to therefore treat them primarily with chemotherapy. Patients with localized disease alone are then subjected to limb-sparing surgery, followed by postoperative chemotherapy with a curative intent. For patients with unresectable disease or metastatic disease at presentation, chemotherapy is used as palliative therapy, and surgical consolidation is reconsidered where enough downstaging of tumor has been accomplished. The specific doses and combinations of chemotherapy need to be individualized for a given patient depending on their age, performance status, and organ function, keeping in mind that a positive dose-response relationship exists for all the active drugs.

Standard regimen Doxorubicin, 75–90 mg/m^2 given as a 96-hour intravenous continuous infusion via a central venous catheter followed by in-hospital cisplatin at 120 mg/m^2 intra-arterially (for extremity/girdle lesions), or intravenously over 2 hours with vigorous hydration and mannitol [11]. Cycles are repeated every 4 weeks for up to four cycles, assuming good tolerance and radiographic response. Patients are then subjected to surgery and the percent necrosis in the resected specimen is assessed. Patients with 95% or higher necrosis receive three to four more cycles of doxorubicin at 75 mg/m^2 as a 72-hour continuous infusion along with ifosfamide at 2.5 g/m^2 over 3 hours daily for 4 days with a 24-hour continuous infusion of mesna. These cycles are repeated at 3-week intervals. Patients who achieve less than 95% necrosis are intensified with ifosfamide, 2.5 g/m^2 over 3 hours each day for 4 days, repeated every 3 weeks for three cycles. This is alternated with high-dose methotrexate at 10 to 12 g/m^2 (target peak methotrexate level higher than 1000 mM) over 4 hours with leucovorin rescue, repeated every 2 weeks for three cycles for a total of three cycles of each regimen.

Contraindications Patients who are not good candidates for this dose-intensive chemotherapy could be considered for single agent chemotherapy at the dose and schedule mentioned above depending on the limitations.

Main side effects Nausea, vomiting, anorexia, fatigue, hair loss, mucositis myelosuppression, cardiac, renal, neurologic dysfunction.

Postradiation soft-tissue sarcomas

Most of these tumors are also high grade and resemble an MFH or an angiosarcoma. Size, grade, and depth are the known prognostic factors for de novo soft tissue sarcomas and are applicable to postradiation sarcomas. Tumors that are superficial and are 5 cm or smaller, regardless of grade, are likely to have a favorable prognosis and are therefore treated with a margin-negative excision. High-grade tumors that are deep and are bigger than 5 cm have a high risk of distant metastases and are therefore preferably treated with systemic chemotherapy followed by a margin-negative excision with a curative intent. Patients with unresectable disease or metastatic disease at presentation are treated with chemotherapy with a palliative intent, and surgical consolidation is reconsidered where enough downstaging of tumor has been accomplished.

Standard regimen Doxorubicin and ifosfamide combination outlined above [12].

Contraindications Patients who are not good candidates for this dose-intensive chemotherapy could be considered for single agent chemotherapy at the same dose and schedule. Alternatives include paclitaxel, specifically for patients with angiosarcoma.

Main side effects As above.

Surgery

- General principles of surgical oncology need to be followed to accomplish a margin-negative excision of the tumor while maintaining as much function as possible. Occasionally, radical surgery becomes necessary to achieve effective palliation.

Radiation therapy

- Standard external beam radiation therapy is usually not a helpful adjunct in these tumors because normal tissue tolerance limits the delivery of another therapeutic dose. The use of brachytherapy or intraoperative radiotherapy needs to be individualized for select cases.

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Review

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Radiation-Induced Malignancies Making Radiotherapy a "Two-Edged Sword": A Review of Literature

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Abstract

Radiotherapy is one of the modalities of treatment of malignancies. Radiation-induced malignancies (RIMs) are late complications of radiotherapy, seen among the survivors of both adult and pediatric cancers. Mutagenesis of normal tissues is the basis for RIMs. The aim of this review of literature was to discuss epidemiology, factors affecting and different settings in which RIM occur.

Keywords: Radiation-induced malignancies; Late side effect; Mutations

Introduction

In medical field, radiation is being commonly used in diagnostic radiology and as therapeutic modality for various malignant as well as non-malignant diseases. During the last few decades, use of radiation has been extensively increased for commercial purposes, e.g. nuclear power plants, disinfectants, agriculture (food preservation and pest control) and others.

One of the worst consequences of radiation exposure is radiation-induced malignancy (RIM). Although the pathogenesis is not well defined, mutation of normal tissues by radiation-induced injury may be the possible mechanism.

Patients cured of primary malignancy have chances of development of various other malignancies (secondary). Radiotherapy may cause mutagenesis in normal tissue and lead to RIM. There are several characteristic features of RIM.

Definition

Cahan's criteria were given by Cahan et al [1] in 1948, which were used to define a radiation-induced sarcoma. They are currently being used as the standard for demonstration of RIM.

The modified Cahan's criteria for diagnosis of RIM are as follows. a) A RIM must have arisen in an irradiated field. b) A sufficient latent period, preferably longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy. c) The treated tumor and alleged induced tumor must have been biopsied. The two tumors must be of different histology. d) The tissue in which the alleged induced tumor arose must have been normal (i.e., metabolically and genetically normal) prior to the radiation exposure.

Atom bomb survivors

Concept of radiation-induced cancer comes from survivors of the atom bomb attacks on Japan. There are two types of radiation emitted from bomb: initial directly emitted radiation and residual radiation. The residual radiations are of two types. First is radiation emitted from induced radioisotopes in soil and metals and second is the nuclear fission products [2].

A number of leukemia cases were noticed in the first few years with peak at 6 - 8 years after the bombings and the relative risk (RR) among children exposed at the age of 10 years was approximately more than 70 times. It is clear that the risk of solid malignancies (bladder, female breast, lung, brain, thyroid gland, colon, esophagus, ovary, stomach, liver and skin (excluding melanoma)) has also increased after the bombing and even persists today [2]. Hall concluded the overall risk of fatal cancers in atom bomb survivors to be 8%/Gy [3].

Histology

Radiotherapy can induce a wide variety of histologic types of malignancy, which cannot be distinguished from natural occurring tumor. In future molecular forensics may have a role in their diagnosis [4, 5]. Carcinoma and leukemias are commonly seen in organs receiving low dose radiation and at regions distant from the treatment site; whereas sarcomas are predominantly seen arising in tissues or organ receiving high dose radiation in or close to the radiation fields [3].

Dose and linear energy transfer (LET)

RIMs are more common with high LET radiation (alpha parti-

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Table 1. RIM After Radiotherapy of Non-Oncological Diseases

Studies	Radiotherapy of non-oncological disease	Type of RIM	Comments
Ron et al [15, 16]	Tinea capitis - radiotherapy to scalp	CNS tumors like meningioma (most common), gliomas, nerve sheath tumor Head and neck malignancies and leukemia	Radiation doses of 1 - 2 Gy can significantly increase the risk of neural tumor
Smith and Doll [17]	Ankylosing spondylitis	Leukemia (most common)	About fivefold increase in deaths from leukemia and a 62% increase in deaths from cancers of sites that would have been in the radiation fields
Albright and Allday [18]	Acne vulgaris	Thyroid malignancies	Thyroid was not shielded during the treatment so received undetermined amount of radiation

cles and neutrons) doses than with low LET (X-rays and gamma rays) doses, especially at low dose rates [6]. The relative biological effectiveness (RBE) for malignant transformation and cytotoxicity increases with increasing LET of the radiation [7].

Energy

RIMs are commonly seen with orthovoltage in comparison to megavoltage radiotherapy. It has been proposed that bone receives a higher dose with orthovoltage radiotherapy and patients receiving this survive longer and thus have higher chance of getting RIM [8].

Age

RIMs are common in children in comparison to adults. It is said that genotoxic injury to the stem cells and longer survival in childhood malignancies may be the reasons behind this phenomenon [9].

Other factors

Factors including chemotherapy, environmental exposure and hereditary predisposition (familial retinoblastoma, tuberous sclerosis, and neurofibromatosis I) can increase the risk of cancer development after radiation exposure [10, 11].

Pathogenesis of RIM

The molecular processes involved in increasing susceptibility and development of RIM are not well understood. Genetic alterations and genomic injury are proposed mechanisms for radiation-induced tumorigenesis in normal tissues. According to Best et al, genome wide association studies (GWASs) have earned some success in identifying significant predictors of cancer susceptibility in cancer survivors [12].

The bystander effect is a phenomenon, which is observed after radiation and chemical exposure, in which the untreated cells demonstrate abnormalities mimicking exposure, such as chromosomal instability, after irradiation [13]. It may be the mechanism of RIM in non-targeted tissues [14].

RIMs After Radiotherapy in Non-Oncological and Oncological Conditions

There are various reports in literature, which show evidence of RIM after radiotherapy of primary disease (non-oncological and oncological).

RIM after radiotherapy of non-oncological disease

Earlier various rheumatologic, infectious and dermatological conditions were treated with low dose radiotherapy which after years led to solid and hematological malignancies (Table 1) [15-18].

Because of longer survival of these patients, they get an adequate latency period to develop RIM in contrast to malignant disorders. In view of this late and adverse side effect, radiotherapy is no longer recommended for the management of non-oncological disease.

RIM after head and neck irradiation

In both definitive and adjuvant settings, radiotherapy is commonly used to treat head and neck carcinoma. The most common histologic sub-types as RIM are squamous cell carcinoma followed by soft tissue sarcoma. In 1989, a study by Cooper et al showed 110 second, independent, malignant tumors out of 928 patients with squamous cell carcinoma of head and neck [19]. Toda et al investigated 322 patients in a retrospective study who had received radiotherapy for early-stage non-Hodgkin's lymphoma (NHL) of the head and neck and found four cases of RIM [20].

RIM after thoracic irradiation

Breast cancer is one of the most common malignancies in females worldwide. Radiotherapy is included in the treatment

Table 2. RIM After Radiotherapy for Breast Cancer

Studies	Site of radiation induced malignancy after radiotherapy for breast cancer	Comment
Deutsch et al [21]	Lung (ipsilateral and contralateral)	Higher dose of radiotherapy to lung in breast cancer patients of NSABP 04 in comparison to NSABP 06 trial was associated with increased incidence of subsequent RIM in both ipsilateral and contralateral lung.
Boice et al [22]	Contralateral breast	The average radiation dose to the contralateral breast in this study was 2.82 Gy and less than 3% of radiation-induced breast cancer could be attributed to previous radiotherapy.
Zablotska et al [23]	Esophagus (squamous cell carcinoma (SCC))	Increases the risk of SCC not adenocarcinoma. As upper and middle third esophagus (commonest site of SCC) not the lower third (commonest site of adenocarcinoma) comes in the radiation portal.
Kirova et al [24]	Sarcomas	Thirty-five out of 16,705 patients of breast cancer developed sarcomas (13 sarcomas were located in the breast, five in the chest wall, three in the sternum, two in the supraclavicular area, one in the scapula, and three in the axilla).

depending upon the stage and histopathological findings. Carcinomas involving lung, contralateral breast, esophagus and sarcoma are the RIMs associated with breast cancer radiotherapy (Table 2) [21-24].

Travis et al concluded that hormonal status is important for radiation-induced breast cancer as ovarian ablation either by radiotherapy or chemotherapy can decrease its incidence [25].

Radiotherapy has a role in the treatment of Hodgkin disease (HD) in case of bulky and residual disease. Decades ago, classic mantle field was designed to treat several nodal stations commonly involved in HD. This broad nodal irradiation causes multiple late toxicities including RIM. Patients surviving HD are considered at higher risk of development of radiation-induced breast, lung and thyroid cancers [26-28].

According to Travis et al, radiation-induced breast cancer after radiotherapy and chemotherapy given for HD depends on the dose of radiotherapy (risk increases with dose), age (common in younger females) and chemotherapy (risk decreases with increasing numbers of alkylating agent cycles) [25].

RIM after pelvic or genitourinary irradiation

RIMs have been reported after pelvic irradiation for cervix, endometrium, prostate and testis (Table 3) [29-32].

RIM after radiotherapy for leukemia

Radiotherapy is used in the treatment of leukemia in the form of prophylactic craniospinal irradiation (PCI) and total body irradiation (TBI). PCI or craniospinal irradiation is a major component of leukemia therapy, typically used for high risk patients and TBI is a standard component of bone marrow transplantation protocols [33, 34].

Tumors of the central nervous system (CNS), followed by leukemias and lymphomas are the most common RIMs seen and the risk of RIMs after radiotherapy persists longer and may be even life-long [35]. According to Neglia et al, meningiomas followed by gliomas are the most common CNS tumors in a case-control study of 14,361 childhood cancer survivors [9].

Radiation-induced meningiomas have following characteristic features, in contrast to sporadic meningiomas. a) Radiation-induced meningiomas are multiple [36]. b) They are aggressive in nature and commonly seen in younger age group [37].

Hematological malignancies like myeloid leukemias can be considered as RIM [38]. According to Boice et al, the risk of leukemia increases with increasing radiation doses up to 4 Gy, then decreases at higher doses [39].

Effect of Radiotherapy Treatment Modality on RIM

Non-therapeutic scatter dose to tissues at a distance from the primary treatment volume has been postulated to be the reason of RIM arising in these areas because of low dose effects and are mainly carcinomas. While RIMs adjacent to the target volume, situated within high dose radiation portal, are generally of sarcomatous histology [40].

Table 3. RIM After Pelvic or Genitourinary Irradiation

Studies	Primary malignancy	Increased risk of RIM
Chaturvedi et al [29]	Cervix	Colon, anus/rectum, bladder, ovary, and genital sites
PORTEC-1 trial [30]	Endometrium	Gastro-intestinal malignancy
Zelefsky et al [31]	Prostate	Skin, bladder and rectum
Van den Belt-Dusebout et al [32]	Testis	Stomach, pancreas, urinary bladder and kidney

Table 4. Risk of Development of RIM

Radiotherapy for primary disease	RIM	Relative risk of development of RIM
Breast [46]	Esophageal cancer	2.19 at 15+ years of radiotherapy
	Lung cancer	1.62 at 10 - 14 years 1.49 at ≥ 15 years
	Myeloid leukemia	2.99 at 1 - 5 years
	Second breast cancer	1.34 at 5 - 10 years 1.26 at 15+ years
Prostate [47]	Rectal cancer	1.26 after EBRT 1.08 after brachytherapy 1.21 after EBRT and brachytherapy
	Bladder cancer	Risk ratio of 1.5
Cervix [3]	Bladder carcinoma	4.5
	Vaginal cancer	2.7
	Non-Hodgkin's lymphoma	2.5
	Rectal cancer	1.8
	Leukemia	2.0
	Carcinoma stomach	2.1
	Bone tumors	1.3
	Uterine malignancy	1.3

Intensity-modulated radiation therapy (IMRT) involves more fields for treatment; as a consequence, a larger volume of normal tissue is exposed to lower doses. In addition, IMRT requires longer beam-on time, which results in increase in the number of monitor units. Both factors are associated with increased integral dose, which tends to increase the risk of secondary malignancies. Therefore, according to Hall, IMRT may increase the incidence of RIM by 0.5% in comparison to the three-dimensional conformal radiation therapy (3D-CRT) [41]. IMRT likely doubles the incidence of RIM (from about 1% to 1.75%) in comparison to the conventional radiotherapy [3]. Combined scatter secondary radiation effects during IMRT delivery with neutron also contribute to out-of-field dose with a deposition pattern independent of the distance to the target treatment field [42].

A decrease in field size decreases normal tissue irradiation. According to Hodgson et al and Sasse et al, decrease in field size is associated with reduced incidence of RIM. By using involved field radiotherapy (IFRT) for HD, radiation-induced breast and lung cancers can be decreased [43, 44].

Fractionation in radiotherapy treatment is responsible for the majority of RIMs. However, a low rate of RIM has also been reported in case of stereotactic radiotherapy [45].

RR of RIM After Radiotherapy

Organs in the vicinity of the primary malignancy show different risk for development of RIM. The factors mentioned earlier (radiosensitivity of organ, planning technique and dosimetry) are mainly responsible for the difference in the RR. After going through the available literature, RRs of RIM in organs adjacent to primary breast, prostate and cervical malignancies, have been summarized (Table 4) [3, 46, 47].

Conclusion

Radiotherapy is an important treatment modality in oncological care. RIMs are considered as one of the most significant and life-threatening late complications of radiotherapy. A number of general conclusions can be drawn from the above discussion.

1) Carcinomas and leukemias are commonly seen in organs receiving low dose radiation; whereas sarcomas are more common in tissues or organ receiving high dose radiation.

2) RIMs are more common with orthovoltage and high LET radiations.

3) Children are at higher risk as compared to adults, with chemotherapy and various hereditary disorders increasing the risk.

4) An increased incidence is observed with IMRT as compared to 3D-CRT due to the dose distribution (larger volume irradiated to lower doses).

Radiation therapy being one of the major treatment modalities of cancer can also sometimes cause cancer, hence truly can be considered a "two-edged sword". RIM is a late and unavoidable side effect of radiotherapy, the exact pathogenesis of which is not well understood. Till date histology of RIM cannot be differentiated from natural occurring tumor.

Conflicts of Interest

All authors declare that they have no conflicts of interest.

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The Management of Radiation-Induced Sarcomas: A Cohort Analysis from a Sarcoma Tertiary Center

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Abstract: (1) Background: Radiation-induced sarcomas (RIS) are rare diseases with poor prognoses. The aim of the study was to analyze outcomes and identify factors affecting survival in a cohort of patients with RIS. (2) Methods: We included consecutive patients with RIS that we found in the available electronic medical records of a sarcoma tertiary center. We analyzed patients' RIS characteristics, management of RIS, the occurrence of local recurrence and distant metastases, the date of disease progression, the date of death, and the date of the last follow-up. (3) Results: Fifty-eight patients met the inclusion criteria. The most frequent sites of RIS development were the thorax and pelvis. The majority of RIS were poorly differentiated, high-grade tumors. Forty patients underwent surgery or radiotherapy with curative intent. The others were referred to palliative chemotherapy. Median progression-free survival and overall survival were 15 and 21 months, respectively. Treatment with curative intent and tumor localization on breasts and upper extremities were associated with a lower risk of death in univariate analysis. (4) Conclusions: The study confirms the poor prognosis of RIS. Treatments with locally curative intent at the tumor site are of prognostic value. Secondary radiotherapy is rarely used in RIS.

Keywords: radiation-induced neoplasms; sarcoma; rare diseases; radiotherapy; cancer survivors; radiation effects

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1. Introduction

Radiation-induced sarcomas (RIS) are iatrogenic malignancies developing after irradiation because of previous cancer or another disease treated with high-dose radiotherapy (RT) [1]. The RIS occurrence rate is 0.03–0.2% at 10 years [2]. The cumulative RIS incidence in the population of patients who received radiotherapy (RT) is 3.2 per 1000 at 15 years, whereas the incidence of primary sarcomas is 2.3 per 1000 in patients who did not receive RT [3]. RIS account for three to six percent of all diagnosed sarcomas [4–8]. However, the incidence is increasing, which may be caused by several factors [9]. First, the reason might be better survival of patients who receive RT because of new systemic therapies, surgical techniques, and other treatment options [10]. Second, the number of indications for RT as a part of organ-sparing, conservative, or definitive treatment increased in the last 30 years; for example, it is indicated for rectal, cervical, breast, and primary soft tissue neoplasms. Third, new, dynamic RT techniques with intensity modulation provide better organs-at-risk sparing, but this occurs at the expense of exposure of larger volumes of healthy tissues to low-dose radiation [11]. That may lead to genomic instability and further malignant transformation [12].

Due to the rarity of RIS, no guidelines nor randomized prospective clinical trials on this topic exist. Thus, the management of RIS is challenging. The only curable modality in non-metastatic RIS is curative resection with wide negative margins [13]. The role of

secondary RT in locally advanced RIS is unclear, mostly due to the concerns about possible severe side effects after re-irradiation. Chemotherapy and targeted therapy may be used in metastatic disease, but their role in the management of localized RIS is not established.

This retrospective study aimed to identify patient, tumor, and treatment characteristics of RIS. Additionally, we evaluated outcomes of treatments and prognostic factors.

2. Materials and Methods

2.1. Analyzed Cohort

We performed a retrospective analysis of a cohort of patients with RIS who were treated in our center between 1998 and 2019. We included consecutive patients with RIS by using modified criteria provided by Huvos et al.: (1) the patient received RT; (2) the neoplasm occurred within the RT volume; (3) a latency period had elapsed; (4) cancer predisposition syndromes such as Li-Fraumeni were excluded [14].

We performed a search for all available electronic medical records through MedStream Designer software from Transition Technologies. Corresponding International Classification of Diseases codes C40, C41, C45, C46, C47, C48, C49, and the keyword "induced" were used. The following parameters were analyzed: patients' characteristics, site and pathological diagnosis of the primary tumor, date of primary RT, date of RIS diagnosis, RIS pathological diagnosis and grade, management of RIS, the occurrence of local recurrence and distant metastases, date of disease progression, date of death, and date of the last follow-up. All available records were reviewed independently by two co-authors. Missing data regarding the date of death, if applicable, were obtained from the National Cancer Registry.

2.2. Statistical Analysis

Follow-up time was calculated using the reverse Kaplan–Meier method. Progression-free survival (PFS) was calculated from the diagnosis of RIS to the last follow-up (censored), disease progression, or death. Overall survival (OS) was calculated from the diagnosis of RIS to the last follow-up (censored) or death. The Kaplan-Meier method for estimating survival functions and the Cox proportional hazards model for estimating the effects of covariates on the hazard of the occurrence of disease progression or death were used. All p values <0.05 were considered significant. The evaluation of data was performed using the R software environment, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), and the jamovi project, version 1.6.14 (retrieved from https://www.jamovi.org, Sydney, Australia).

3. Results

3.1. Patients' Characteristics and RIS Diagnosis

Fifty-eight patients met the inclusion criteria. Forty-three of them were female, and 15 were male. Median follow-up time was 15 months (interquartile range (IQR): 9–24 months), with a maximum of 230 months. The most frequent sites of both primary cancer and RIS were the thorax and pelvis. The group comprised soft tissue sarcomas (79%) and bone sarcomas (21%). The vast majority of RIS were poorly differentiated, high-grade tumors. The most frequent pathological diagnoses were undifferentiated pleomorphic sarcoma (24%) and sarcoma not otherwise specified (21%). Tables 1 and 2 provide a summary of primary tumor patients' data and RIS.

Table 1. Primary tumor characteristics.

Characteristic		Value
Age at Primary Radiotherapy	Median (Range)	43 (3–76) Years
		Number of enrolled patients (%)
Sex	Male	43 (74)
	Female	15 (26)
Received treatment	Radiotherapy	35 (60)
	Radiochemotherapy	25 (40)
Primary cancer	Breast cancer	20 (35)
	Sarcoma	11 (19)
	Other	10 (17)
	Hodgkin lymphoma	8 (14)
	Uterine cancer	5 (9)
	Non-Hodgkin lymphoma	4 (7)
Primary site (most of irradiated volume)	Thorax	19 (33)
	Pelvis	18 (31)
	Breast	11 (19)
	Head and neck	4 (7)
	Central nervous system	2 (3)
	Upper extremity	2 (3)
	Lower extremity	2 (3)

3.2. RIS Management

Forty-eight patients were preliminarily amenable to curative treatment. The others (n = 10) were locally too advanced for curative treatment (n = 9) or had synchronous distant metastases at the moment of diagnosis of RIS (n = 1); all but one of them received palliative chemotherapy. Among the patients who were eligible for curative treatment, eight did not respond to induction chemotherapy (n = 7) or radiochemotherapy (n = 1) and were locally too advanced to undergo curative surgery or RT; those patients were referred to palliative treatment. One patient received curative RT combined with chemotherapy as seen in Figures S1 and S2. Thirty-nine patients underwent surgery with curative intent. Among them, R0, R1, and R2 resections were obtained in 18, 14, and 1 patient, respectively. In six cases, margin status was not available. The applied methods of treatment are summarized in Figure 1.

Table 2. Radiation-induced sarcoma characteristics.

Characteristic		Value
Age at RIS Diagnosis	Median (Range)	57 (20–84) Years
Years from primary RT to RIS diagnosis	Median (range)	11 (3–36) years
		Number of enrolled patients (%)
RIS site	Thorax	22 (38)
	Pelvis	15 (26)
	Breast	5 (9)
	Head and neck	4 (7)
	Upper extremity	4 (7)
	Abdominal cavity	3 (5)
	Lower extremity	3 (5)
	Central nervous system	2 (3)

Table 2. *Cont.*

Characteristic		Value
RIS pathology	UPS	14 (24)
	Sarcoma NOS	12 (21)
	Osteosarcoma	9 (16)
	Angiosarcoma	7 (12)
	Fibrosarcoma and myxofibrosarcoma	6 (10)
	MPNST	4 (7)
	Leiomyosarcoma of the bone	1 (2)
	Chondrosarcoma	1 (2)
	Malignant GCT of the bone	1 (2)
	Synovial sarcoma	1 (2)
	Pleomorphic liposarcoma	1 (2)
	Round cell sarcoma	1 (2)
RIS grade	1	3 (5)
	2	16 (28)
	3	39 (67)

GCT—giant cell tumor; MPNST—malignant peripheral nerve sheath tumor; NOS—not otherwise specified; RIS—radiation induced sarcoma; RT—radiotherapy; UPS—undifferentiated pleomorphic sarcoma.

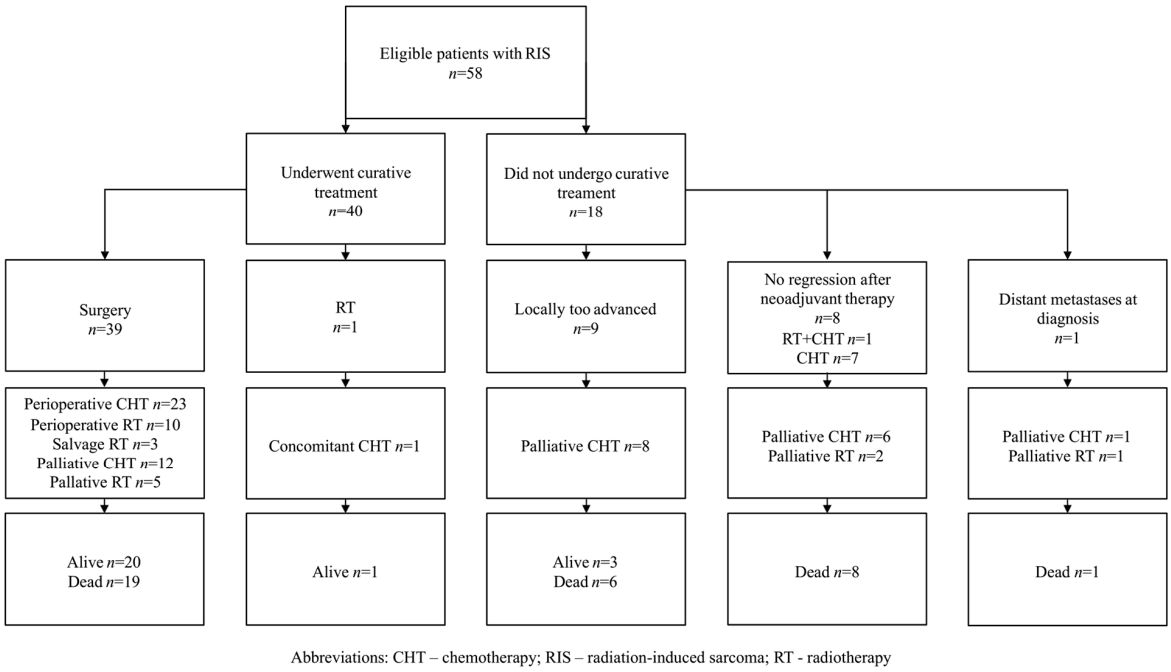

Figure 1. Applied methods of treatment in analyzed cohort.

3.3. Survival Analysis

At the moment of analysis, 24 patients were alive (41%). New distant metastases were observed in 16 cases. Local recurrence after curative treatment occurred in 18 cases. Median PFS was 15 months (95% confidence interval (CI) 11–21 months). Five-year PFS was 22% (95% CI 12–42%). Median OS reached 21 months (95% CI 18–47 months). Five-year OS was 17% (95% CI 8–37%). In the univariate analysis, we found a strong influence of curative treatment to hazard ratio (HR) on death (HR 0.21, $p < 0.001$). Moreover, RIS that developed in the breasts and upper extremities were associated with a lower risk of death (HR 0.09, $p = 0.05$ and HR 0.06, $p = 0.026$, respectively) in the univariate analysis (see Table 3). Due to

the relatively small number of patients (n = 58) and the low number of events (n = 33), we abandoned the multivariate analysis.

Table 3. Hazard ratios for death with 95% confidence intervals and p-values calculated from a univariate Cox proportional hazards model for all enrolled patients.

		Number of Cases	Hazard Ratio	95% Confidence Interval	p-Value
Primary treatment	radiotherapy	35	1		
	radiochemotherapy	23	1.16	0.58–2.32	0.675
RIS site	central nervous system	2	1		
	head and neck	4	0.19	0.03–1.40	0.104
	thorax	22	0.29	0.06–1.33	0.111
	breast	5	0.09	0.01–1.00	0.050
	upper extremity	4	0.06	0.01–0.71	0.026
	abdominal cavity	3	0.62	0.09–4.54	0.641
	pelvis	15	0.36	0.08–1.70	0.196
	lower extremity	3	0.68	0.09–4.84	0.697
RIS pathology	osteosarcoma	9	1		
	NOS	12	1.67	0.54–5.15	0.375
	UPS	14	1.43	0.44–4.64	0.550
	angiosarcoma	7	1.03	0.24–4.50	0.966
	myxo/fibrosarcoma	6	1.01	0.23–4.39	0.986
	MPNST	4	1.30	0.34–4.95	0.703
	other	6	1.07	0.25–4.52	0.926
Grade	1	3	1		
	2	16	1.62	0.20–13.01	0.652
	3	39	2.27	0.30–16.88	0.424
Locally curative treatment	no	18	1		
	yes	40	0.21	0.10–0.44	<0.001

MPNST—malignant peripheral nerve sheath tumor; NOS—sarcoma not otherwise specified; RIS—radiation-induced sarcoma; UPS—undifferentiated pleomorphic sarcoma.

Median OS differed between patients who underwent treatment with curative intent and those who did not (37 vs. 13 months, $p < 0.0001$; see Figure 2a), and between patients who underwent curative surgery and those who did not (37 vs. 15 months, $p < 0.0001$; see Figure 2b).

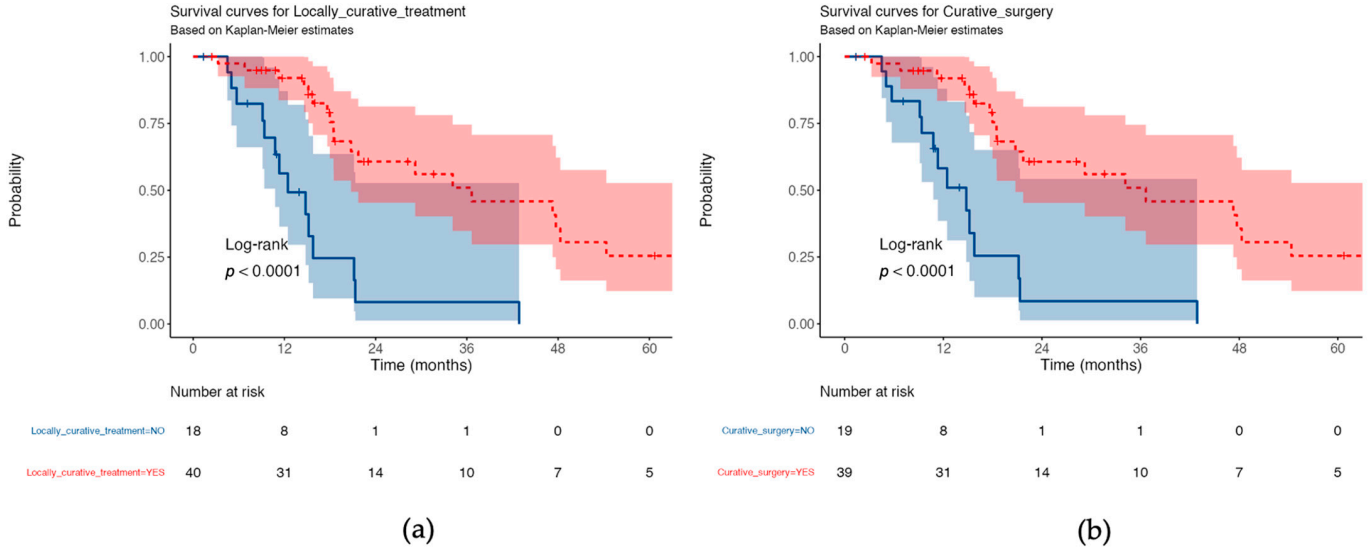

Figure 2. Overall survival curves with 95% confidence intervals for all enrolled patients: (**a**) locally curative treatment vs. no locally curative treatment; (**b**) curative surgery vs. no curative surgery.

In the univariate analysis, we did not find an influence of surgical margins and perioperative treatment to HR on death in the subgroup of patients treated with curative surgery (see Table 4).

Table 4. Hazard ratios for death with 95% confidence intervals and *p*-values calculated from a univariate Cox proportional hazards model for patients who underwent curative surgery.

		Number of Cases	Hazard Ratio	95% Confidence Interval	*p*-Value
Perioperative radiotherapy	no	29	1		
	yes	10	1.31	0.51–3.36	0.568
Perioperative chemotherapy	no	16	1		
	yes	23	0.86	0.34–2.15	0.742
Surgical margin	R0	18	1		
	R1	14	1.14	0.39–3.28	0.813
	R2	1	4.12	0.47–36.04	0.201
	unknown	6	2.71	0.79–9.35	0.114

R0—microscopically negative margins; R1—microscopically positive margins; R2—gross residual disease.

4. Discussion

RIS are very rare entities that may develop several years after primary RT. In our study, the median latent period was 11 years. RIS in our cohort presented aggressive tumor subtypes and behavior, being intermediate or high-grade in the vast majority of cases (95%). Despite diagnosis at an early or locally advanced stage and intensive treatment, results remain unsatisfactory, with a median OS as low as 21 months. The only factor strongly impacting survival is surgery with curative intent. Similar findings were reported in a recently published cohort analysis of RIS [15]. However, we did not find an influence of obtained margins and perioperative treatment on OS in a group of patients treated with curative surgery. Interestingly, perioperative chemotherapy was used more frequently than secondary RT in a previously irradiated volume (59% vs. 26%), although guidelines recommend perioperative RT in the majority of locally advanced or high-grade primary soft tissue sarcomas [16,17].

Data concerning RIS remain greatly limited. Available larger series describe RIS epidemiology or cohorts of breast cancers survivors, but only a few focus on treatment

regimens [5,18–23]. All available reports highlight the poor prognosis for patients with RIS, which is in concordance with results from the current study. Importantly, in the two studies, survival rates in RIS were reported as worse than in sporadic soft tissue sarcomas [13,18].

In our study and other cohorts, the most frequent site of RIS development is the thoracic region, which is frequently irradiated due to breast cancer or Hodgkin lymphoma. Those neoplasms are associated with long life expectancy and a higher risk of RIS. The pathological pattern of thoracic RIS in our cohort confirms the high occurrence of angiosarcoma (24%), a sarcoma subtype strongly associated with the previous treatment of breast cancer [20,24]. Although it may seem like the number of radiation-induced angiosarcomas in our cohort is low, the majority of them are usually treated in breast cancer units outside sarcoma tertiary centers. Interestingly, in the current study, RIS localized in the breast and upper extremities were associated with a lower risk of death. This could be explained by the greater possibility of performing curative surgery with adequate margins, up to mastectomy or extremity amputation.

Nevertheless, pathological subtypes in the entire current cohort of patients with RIS are similar to those presented in other cohort studies with RIS that focus on results of treatment [15,19]. However, in our series, obtained surgical margins did not affect patients' survival; whereas, in the aforementioned cohorts, gross positive resection margin was predictive for poorer survival. This discrepancy may be explained by the different approaches preferred by multidisciplinary tumor boards in sarcoma reference centers. In the current study, R2 margin was present only in one patient. In the study published by Cha et al., 32% of patients had gross positive margins [19]. In turn, in our study, 67% of patients underwent curative surgery, as compared to 90% in the aforementioned report. That may suggest distinct criteria of resectability in both institutions.

Surgery with curative intent is a mainstay of therapy. However, it may not be feasible due to anatomical location, fibrotic changes after previous irradiation, multifocal disease, or invasion of surrounding vital organs. In the current study, among patients who did not undergo surgery, nine were locally too advanced to receive such treatment and were referred to palliative chemotherapy. The other eight patients did not achieve satisfactory local response to induction treatment to undergo curative surgery. Importantly, in this combined subgroup, only one patient received preoperative RT. It has been shown that preoperative RT alone or combined with systemic treatment may provide substantial benefits to locally advanced soft tissue sarcomas [25–27]. RT is not frequently used in previously irradiated volumes due to the risk of significant toxicity, lack of appropriate knowledge about tolerance doses, and unknown repair of healthy tissues several years after primary RT. Additionally, there could be a strong psychological barrier related to re-irradiation. Patients may refuse secondary RT, fearing the treatment modality that caused RIS.

Moreover, RT techniques and regimens constantly evolve, and it is frequently impossible to reassess dose distribution that was delivered 20 or more years ago using other RT methods. However, RT may be carefully used in selected patients. An interesting approach could be a combination of RT with local or regional hyperthermia that enhances oxygenation and inhibits repair of RT-related damage in sarcoma cells [28–30]. In a retrospective cohort analysis, the authors presented the results of re-irradiation combined with hyperthermia of 16 patients with RIS in the thoracic area, which is the most frequent site of RIS development [31]. The most represented pathology was angiosarcoma (69%). In 12 patients who were eligible for assessment, the response rate was 75%, including seven complete responses and two partial responses. Only one patient developed severe late toxicity, which resulted in forearm amputation five years after treatment. Among the remaining patients, the authors described mild, late toxicities in six of them. Currently, one prospective clinical trial evaluates the combination of hypofractionated RT with hyperthermia in radiation-induced or recurrent soft tissue sarcomas (NCT04398095) [32].

This study has weaknesses. The obtained sample of patients may not be representative due to a selection bias caused by the retrospective nature of the analysis. To minimize the

effect of selection, all data were reviewed by two co-authors independently (MJS, AMC). Moreover, with the retrospective nature and the presence of events that occurred decades ago, there is a significant risk of incomplete data or data misinterpretation. Additionally, the soft tissue and bone tumor classifications, available diagnostic tools, RT techniques, and treatment methods have changed in the last 30 years. Therefore, our cohort might not be representative of the contemporary population. Nevertheless, due to the long period of RIS development after RT, the aforementioned situation is inevitable. Another weakness of the study is the lack of precise RT data and dose distribution analysis, which could also be prognostic factors. RT details might have provided important data for further RT planning recommendations, especially for patients with expected long-term survival and risk of RIS development. However, the aforementioned data were poorly available or unavailable due to the long period from RT for a primary tumor or RT performed outside our center; the earliest RT in our cohort was applied in 1976. Unfortunately, the National Cancer Registry provides only data regarding patients' survival, while old information regarding primary tumors is not available. In summary, the results of the analysis should be interpreted with caution. Despite that, this study can provide valuable data on this important topic due to the relatively large sample size with this very rare entity.

Due to the rarity of RIS and lack of guidelines, it would be highly advisable for patients to participate in clinical trials. However, access to sarcoma-dedicated trials could be limited by the frequent exclusion of patients with a history of RT in the affected area or history of second active malignancy with a required long, disease-free period. Thus, data collection in prospective registries may be an alternative approach.

5. Conclusions

Despite intensive treatment, the prognosis of RIS remains poor. Surgery with curative intent remains the basic method of RIS management. However, the optimal treatment regimen and the role of other modalities are not established. Secondary RT is rarely used in RIS. The development of new clinical trials or prospective registries should be encouraged.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/4/694/s1, Figure S1: Dose distribution of summed plan (reirradiation, transverse view), Figure S2: Dose distribution of summed plan (reirradiation, frontal view).

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Informed Consent Statement: Patient consent was waived due to retrospective character of the analysis. The paper does not report on the use of experimental or new protocols.

Data Availability Statement: All data generated or analyzed during this study are available upon reasonable request.

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