Radiation-Induced Soft Tissue Sarcoma

Sana Intidhar Labidi-Galy, MD
Louis Tassy
Jean-Yves Blay, MD, PhD
ABSTRACT
Radiation-induced soft tissue sarcomas (RIS) are rare clinical entities. Their incidence increases as survival after radiotherapy improves, and they often constitute a therapeutic challenge. RIS generally develop with a median latency period of 10 years and encompass different histological types. The majority of RIS are high-grade and deep tumors. Large size and positive histologic margins after surgery are responsible for high local relapse rates and short survival. Surgery remains the primary treatment option for localized disease and often requires an aggressive approach. This article provides an overview of the clinical manifestations, prognosis, imaging and treatment of RIS.

BACKGROUND
Approximately 60% of all patients with cancer will receive radiotherapy during the course of their disease. Unfortunately, a second malignancy can develop years later as a result of this life-saving therapy.

A recent UK study estimated that 1,346 cases of cancer, or about 0.45% of the 298,000 new cancers registered in the UK in 2007, were associated with radiotherapy for a previous cancer. The largest numbers of radiotherapy-related second cancers were lung cancer (23.7% of the total), esophageal cancer (13.3%), and female breast cancer (10.6%). The highest percentages of second cancers related to radiotherapy were among survivors of Hodgkin’s disease and cancers of the oral cavity, pharynx and cervix uteri. Similarly, a population-based, retrospective review of the Surveillance, Epidemiology and End Results (SEER) database showed elevated risks of breast, lung, and other cancers among young patients given radiotherapy for Hodgkin lymphoma. Although radiogenic cancers were not common following most adult-onset malignancies, excess risks were seen for cancers of the lung and esophagus, as well as sarcomas, following initial radiotherapy for breast cancer.

Radiotherapy has been demonstrated to play a causative role in the pathogenesis of sarcomas from the early 1900’s. In 1904, Perthes described the association between radiotherapy and sarcomas in a patient who developed a spindle-cell sarcoma following radiation for lupus, a long-term autoimmune disorder that may affect the skin, joints, kidneys, brain, and other organs. RIS were subsequently defined by Cahan et al as lesions of different histology to that of non-irradiated sarcomas, arising within a previous radiotherapy field usually after a latency period of more than four years. Since that time, few advances have been made toward elucidating the molecular pathogenesis of these diseases.

RIS are a well-known treatment complication and constitute about 3% of all sarcomas. The most comprehensive study to date found the cumulative incidence of metachronous sarcoma to be 3.2 per 1000 at 15 years post-diagnosis. This is an important subgroup, as these cancers are iatrogenically incurred, often in patients who have achieved “cure” from their primary malignancy.

It has been suggested that the incidence of RIS is increasing. Likely reasons for this include survival of irradiated patients as a result of systemic chemotherapy and increased use of
therapeutic irradiation, particularly in the treatment of breast cancer. Breast conservation with radiotherapy is now widely employed for symptomatic malignancy. Population-based screening for breast cancer has resulted in earlier diagnosis and increased survival of a cohort of patients who are now treated with breast conservation and radiotherapy. Without screening, it is likely that those patients would have fared worse and may have been treated by mastectomy alone. In a SEER database review, Huang et al showed a 16-fold increase in angiosarcoma in radiotherapy patients versus controls and a two-fold increase in all soft-tissue sarcomas (STS) in radiotherapy patients.

Newer technologies, such as intensity-modulated radiation therapy (IMRT), involve the use of more fields and consequently expose more normal tissue to low-dose radiotherapy. To deliver a specific dose to the center of the tumor, IMRT requires the accelerator to be energized longer, which results in higher radiation doses. Therefore, it has been estimated that the incidence of RIS may increase by 0.5% with IMRT.

**RISK FACTORS FOR RIS**

Identified risk factors for developing RIS are young age at treatment and treatment-related factors, including high radiation dose and simultaneous chemotherapy with alkylating agents. Patients' genetic constitution can also predispose them for second cancers, independently of previous radiotherapy, as in patients with previous retinoblastoma or in the Li-Fraumeni syndrome.

*Retinoblastoma* is a rare type of eye cancer that usually develops in early childhood, typically before the age of five. This form of cancer develops in the retina. Most cases of retinoblastoma are due to mutations of the Rb1 gene. It is often curable when it is diagnosed early.

*Li-Fraumeni syndrome* is a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults. The cancers most often associated with Li-Fraumeni syndrome include breast cancer, a form of bone cancer called osteosarcoma, and cancers of the soft tissues (such as muscles) called soft-tissue sarcomas (STS). The CHEK2 and TP53 genes are associated with Li-Fraumeni syndrome.

Although a clear dose-response relationship for radiation-associated malignancies is not established, it is generally accepted that carcinomas arise in tissues exposed to lower doses, whereas sarcomas are induced in heavily radiated tissues in or close to the radiation fields.

Radiation doses above 50 Gy cause cell death, while lower doses (<30 Gy) cause genomic instability (defects in genes relating to DNA repair leading to increased DNA alterations) and damage cell repair mechanisms. RIS typically occur within or at the edge of the radiation field. At the edge of the radiation field, the dose of radiation is not homogeneous and may be less than the tumor killing dose. This may enable surviving genetic mutations to progress into developing tumors. The latency period appears inversely related to dose, but there are reports to the contrary.

**Gray (Gy) Unit:** The gray measures the deposited energy of radiation. It is defined as the absorption of one joule of ionizing radiation by one kilogram of matter (usually human tissue).
DEFINING RIS
The definition of radiation-induced sarcomas (RIS) has never been well established. The generally accepted criteria of RIS proposed by Cahan and modified by Arlen et al are:
1. treatment with therapeutic irradiation at least three years prior to development of sarcoma
2. a sarcoma arising within the field of previous therapeutic irradiation
3. differing histology between the sarcoma and the primary tumor that required radiotherapy

The length of time between radiation exposure and sarcoma formation is the major criterion that has been modified by most investigators. It was recently suggested by the sarcoma team at Memorial Sloan Kettering Cancer Center (MSKCC) that a latency of six months is sufficient to affirm the diagnosis of RIS, which contrasts with the generally accepted time frame of several years.

PROGNOSIS
RIS are aggressive tumors, and the prognosis is thought to be worse than for traditional STS. A recent study from the MSKCC suggests that radiation-induced sarcomas are an independent prognostic factor associated with worse outcome, when compared to traditional STS, in a multivariate analysis that adjusted for age, tumor size, depth and margin status. The estimated five-year survival of RIS varies between 17% and 58%. Most published studies agree that the five-year survival rate of RIS patients is significantly lower than that of patients with de novo STS.

Clinical and pathological characteristics of RIS can also explain the poor outcome of this disease, including a majority of deep, large (>5cm) and high grade tumors. In addition, RIS's propensity for central rather than peripheral locations probably contributes to its unfavorable outcome due to poor surgical accessibility.

In the three larger series of RIS, it appears difficult to obtain microscopically negative resection (R0). This data indicates that achieving negative histological margins is challenging in this disease. As a consequence, local relapse rates are high at about 45% and are a major contributor to mortality. Previous therapy may reduce treatment possibilities, as repeated high-dose radiotherapy often is impossible, and chemotherapy is limited by bone marrow dysfunction.

CLINICAL PRESENTATION
RIS are aggressive tumors, and the prognosis is thought to be worse than for traditional STS. A recent study from the MSKCC suggests that radiation-induced sarcomas are an independent prognostic factor associated with worse outcome, when compared to traditional STS, in a multivariate analysis that adjusted for age, tumor size, depth and margin status. The estimated five-year survival of RIS varies between 17% and 58%. Most published studies agree that the five-year survival rate of RIS patients is significantly lower than that of patients with de novo STS.

Emphasis can be placed on understanding breast angiosarcoma post-radiation and breast-conserving therapy (BAPBCT). It accounts for 0.5% of patients undergoing a breast-conserving strategy for breast cancer. BAPBCT can present as reddish-purple patches with a hematoma-like appearance, or as a palpable tumor, purple plaques or erythematous nodules. The median latency interval is 10 years and is shorter than the interval from lymphedema to angiosarcoma (Stewart-Treves Syndrome).
Some patients develop atypical vascular proliferation (AVP) that does not meet pathologic criteria for angiosarcoma but may represent a precursor lesion or incipient angiosarcoma. This type of AVP usually presents as one or more small, flesh-colored papules or erythematous patches that arise in radiated skin. The current recommendation is that AVP should be completely excised and the patient closely followed up for any new lesions.

**Atypical Vascular Proliferation (AVP)** is the benign version of postradiation vascular tumors. The histology and clinical presentation of AVP can mimic angiosarcoma, and repeated biopsies may be required to clearly distinguish these two entities.

**DIAGNOSIS**

**Imaging**

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) are the imaging modalities of choice to evaluate and follow RIS or to look for distant spread of the disease (Figure 2). Imaging features of RIS are not pathognomonic and can be difficult to interpret. It can be very difficult to exclude a recurrence of the primary tumor when relying on imaging alone.

**Pathological Findings**

As with all STS, core needle biopsy is mandatory in confirming the diagnosis of RIS. The biopsy will distinguish between a new sarcoma, recurrence of the primary malignancy, and post-operative or post-radiotherapy changes. Biopsy will also indicate the histologic subtype and grade of the sarcoma.

All histologic subtypes can be observed as RIS, but their frequency varied from those of de novo STS. It seems that malignant fibrous histiocytoma (MFH), a controversial entity pooling undifferentiated pleomorphic sarcomas not otherwise specified, are the most common subtype. Other frequent subtypes include angiosarcoma (with a majority of BAPBCT), leiomyosarcoma and fibrosarcoma. Extra-skeletal osteosarcoma is a rare spontaneous tumor constituting 2-4% of all osteosarcomas, but it seems to be more common among RIS. In contrast, the number of radiation-induced liposarcomas is very low, even though liposarcoma belongs to the most common histological subtype of STS.
While the median size of RIS tumors is no greater than that of other sarcomas, the proportion of high grade RIS tumors is greater, more than 80% in most of series. Tumor necrosis, a known unfavorable factor judged by light microscopy, is also present in the majority of RIS.

Sarcomas after radiotherapy of testicular cancer represent a diagnostic challenge. Sarcomatous foci may be present within primary testicular germ cell tumors. If sarcoma occurs within the field of radiotherapy after the treatment of a testicular germ cell tumor, it is important to determine if it is a new sarcoma (RIS) or a relapse of the primary tumor that contained sarcomatous foci.

Two studies \(^{33,34}\) have investigated the role of KIT in RIS. KIT is a transmembrane receptor tyrosine kinase, which is involved in cell signal transduction and plays a major role in the oncogenesis of gastro-intestinal stromal tumors (GIST). KIT was expressed in the majority of RIS (88%)\(^{34}\), in particular angiosarcoma, whereas only 22% of spontaneous STS express this protein. However, the authors did not find the activating mutation in the KIT gene. Importantly, expression of the KIT protein does not mean that therapy with a tyrosine kinase inhibitor is indicated.

**Molecular Biology**

Very little is known about the genetic changes involved in the tumorigenesis of postirradiation sarcomas. According to a recent study and review by Mertens et al regarding cytogenetic changes in RIS\(^ {35}\), these tumors have complex karyotypes, with loss of 3p21-pter being more frequent than in sporadic sarcomas. Also, polyclonal tumors with near-diploid chromosome numbers (few or no karyotypic abnormalities) were observed.\(^ {35}\) Additional cytogenetic studies and reviews pointed out two distinct patterns:

1. Polyclonal karyotypes, often with simple and balanced translocations, preferentially observed after long-term culturing.
2. Monoclonal chromosomal alterations observed in highly aneuploid and complex karyotypes, usually detected in short-term cultures or in xenografts.\(^ {36}\) Alterations of the RB1 and TP53 tumor suppressor genes, also called antioncogenes, are frequent.\(^ {37,38}\) According to a study by Nakanishi et al,\(^ {37}\) the frequency of TP53 mutations is higher in RIS than in sporadic sarcomas. Gains at 7q or 8q are associated with poor prognosis or large tumor size.\(^ {39}\)
Recently, a genomic study using array-comparative genomic hybridization as a screening method reported high-level amplification of MYC on chromosome 8q24.21 This recurrent genetic alteration was found in 55% of postirradiation angiosarcoma or chronic lymphedema, but not in primary angiosarcoma. Amplification of MYC did not predispose to high grade morphology or increased cell turnover.

**TREATMENT**

**Surgery**

It is unclear whether treatment should be modified in RIS versus traditional STS. Radical resection with negative histological margins (R0) is the treatment of choice for localized disease (Figure 3). Surgical resection includes wide excision, limb-sparing surgery or forequarter amputation. Previous irradiation impairs anatomic and tumor planes, preventing surgeons from appreciating true tumor margins. This further reinforces the necessity for aggressive and wide resection, especially considering that a positive surgical margin will reduce survival by nearly half.

![Figure 3](image)

**Figure 3:** Microscopic exam of a localized spindle cell sarcoma developed in the pectoralis major muscle and totally resected with negative margins. (A): The surgeon resected the pectoralis major muscle. (B): Cross section revealed a well-circumscribed mass.

Major plastic surgical reconstruction can be required, ranging from split thickness skin grafting to local flaps and free tissue transfer. Sometimes it is necessary to reconstruct the chest or abdominal wall using a polypropylene mesh and methyl methacrylate sandwich technique. Due to the high incidence of multifocal RIS after breast cancer treatment, in particular BAPBCT, a surgeon might consider removing the entire irradiated area and not just the tumor.

**Radiation Therapy**

Additional radiation therapy using modern techniques may be considered, but there are concerns about toxicity, as repeated high-dose radiotherapy is often impossible due to limited bone marrow function. Data from case reports have been published on hyperfractioned radiotherapy for BAPBCT showing certain efficacy. BAPBCT tumors have a high growth rate, making them more likely to repopulate between daily fractions of radiotherapy. The use of multiple daily fractions might, therefore, prevent repopulation from occurring.

**Chemotherapy**

For metastatic disease, palliative chemotherapy using single agent doxorubicin remains the treatment of choice for the majority of RIS. Paclitaxel and anti-angiogenic drugs, such as sorafenib and sunitinib, have shown some efficiency in angiosarcomas.
Trabectidine (ET-743) is a novel compound that acts by inhibiting cell-cycle transition from the G2 to M stages. Trabectidine is an interesting option in RIS, particularly for patients who received prior chemotherapy with anthracyclines for primary tumors such as lymphomas and breast cancers.

Chemotherapy can be administered in the neoadjuvant setting, before surgical resection, to improve local control and eradicate subclinical metastatic disease.

SURVEILLANCE
Patients with RIS should be followed just as all STS patients are. Quarterly visits to the physician, with or without imaging, are typically warranted for the first two years. After two years, semi-annual visits are performed until the five-year anniversary.

CONCLUSION
Since the majority of cancer patients receive radiotherapy, it is critical that clinicians are aware of the potential development of RIS, which can occur decades after radiotherapy. Any abnormality should be biopsied, and if a sarcoma is detected, the treatment of choice for RIS is surgical resection with negative margins. Future studies analyzing clinical and pathological characteristics of primary tumors, and breast cancers in particular, can help to identify factors that predispose to RIS for better selection of patients undergoing radiotherapy. Another issue is to examine is the genetics of RIS, which may illuminate the mechanisms responsible for sarcomagenesis.

REFERENCES


Also Available at SarcomaHelp.org

Articles about Sarcoma Diagnosis and Treatment
A Guide to the Sarcoma Universe
Coping with Sarcoma
Guidelines for Patients, Caregivers & Doctors
Guidelines for Parents of Pediatric Patients
Sarcoma Centers
Second Opinions
Side Effects of Treatment

Articles about Specific Types of Sarcoma
Alveolar Soft Part Sarcoma    Angiosarcoma
Clear Cell Sarcoma           Chondrosarcoma of the Bone
Dermatofibrosarcoma Protuberans DSRCT
Epithelioid Sarcoma          Ewing's Sarcoma
Fibrosarcoma of Bone         Leiomyosarcoma
Leiomyosarcoma of the Uterus Liposarcoma
Malignant Fibrous Histiocytoma Mesenchymal Chondrosarcoma
MPNST                        Osteosarcoma
Rhabdomyosarcoma             Synovial Sarcoma

Articles about Sarcoma Research
A Research Roadmap           Cancer Stem Cells
Chromosomal Translocations   Epigenetics
Gene Profiling               Immunotherapy
Mouse Models                 Nanotechnology
Targeted Therapies           The State of NCI Funding

Articles about Current Research Studies
A Preclinical Mouse Model for Uterine Leiomyosarcoma
Deep Exome Sequencing to Identify the Gene Causing Solitary and Ollier
Chondrosarcomas
Genomic and Molecular Characterization of EGFR and IGF1R as Key Potential
Therapeutic Targets in Malignant Peripheral Nerve Sheath Tumors
Targeting the PI3K/AKT Pathway in UPS/MFH : Aiming Towards Novel Therapy
Targeting the Tumor-associated Antigen p27kip1 in Metastatic Osteosarcoma
Translational Research in Well-Differentiated and De-Differentiated Liposarcoma
Electronic Sarcoma Update Newsletter

ESUN is an online, peer-reviewed newsletter that contains articles of interest to patients, caregivers, physicians and nurses. ESUN’s feature articles discuss specific sarcomas and the issues involved in dealing with these rare cancers. Regular columns cover clinical trials, recent research findings, community news, patient stories, and a variety of topics of interest to the sarcoma community.

ESUN was first published in 2003, and each issue is accessed by thousands of readers worldwide.

MEDICAL EDITORIAL AND ADVISORY BOARD
Laurence Baker, DO, Southwest Oncology Group and SARC
Jean-Yves Blay, MD, PhD, Université Claude Bernard in Lyon, France
Murray Brennan, MD, Memorial Sloan-Kettering Cancer Center
Frederick (Fritz) Eilber, MD, UCLA Medical Center
Mark Gebhardt, MD, Harvard University, Beth Israel Deaconess Medical Center
Richard Gorlick, MD, The Children’s Hospital at Montefiore
Alessandro Gronchi, MD, Istituto Nazionale Tumori in Milan, Italy
Mary Louise Keohan, MD, Memorial Sloan-Kettering Cancer Center
Crystal Mackall, MD, National Cancer Institute
David Malkin, MD, The Hospital for Sick Children in Toronto, Canada
Ole Steen Nielsen, MD, University of Aarhus in Aarhus, Denmark
Raphael Pollock, MD, PhD, University of Texas M. D. Anderson Cancer Center
R. Lor Randall, MD, University of Utah, Huntsman Cancer Institute
Piotr Rutkowski, MD, PhD, Sklodowska-Curie Memorial Cancer Center in Warsaw, Poland
Peter Schlag, MD, PhD, Charité University Hospital in Berlin, Germany
David Thomas, MD, Peter MacCallum Cancer Centre in East Melbourne, Australia
Margaret von Mehren, MD, Fox Chase Cancer Center
Leonard Wexler, MD, Memorial Sloan-Kettering Cancer Center
Jeremy Whelan, MD, University College Hospital in London, United Kingdom

SUBMITTING AN ARTICLE
For information on submitting an article and a copy of our current publication calendar, please contact bruce@sarcomahelp.org.

ABOUT THE LIDDY SHRIVER SARCOMA INITIATIVE
The mission of the Liddy Shriver Sarcoma Initiative is to improve the quality of life for people dealing with sarcoma. The Initiative increases global public awareness of sarcoma, raises funds to award research grants, and provides support and timely information to sarcoma patients, their families, and medical professionals. These efforts are achieved through collaboration with numerous individuals and organizations that share a similar vision.