# RADIATION-INDUCED SARCOMA OF THE BREAST: A REVIEW

By

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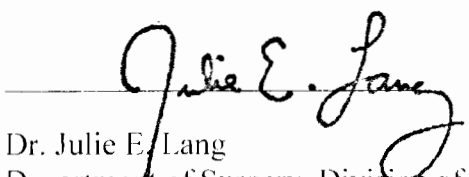

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**ABSTRACT**

**Radiation induced sarcomas (RIS) are rare, aggressive malignancies. Breast cancer survivors treated with radiation therapy constitute a large fraction of patients with RIS. We performed a systematic review of the published English literature in an effort to evaluate evidenced based practices for the treatment of RIS. Our systematic review identified 115 original articles available for analysis. Using the hierarchal levels of evidence, we classified these articles based on their levels of scientific evidence. This review critically evaluates the current published literature on the treatment of RIS in an effort to establish evidenced based practices for this rare disease.**

## Introduction

Radiation therapy is an important modality for the treatment of primary breast cancer. Radiation-induced sarcomas (RIS), a rare iatrogenic malignancy, can occur after breast cancer treated with radiation and typically confer poor outcomes. For patients receiving radiotherapy for the treatment of breast cancer, the cumulative incidence of a malignant sarcoma was 3.2 per 1000 at 15 years compared to 2.3 per 1000 for patients not receiving radiotherapy[1]. With relatively few reported cases, radiation induced sarcomas (RIS) have a low occurrence rate ranging from about 0.03%- 0.2% over a 10 year period [2-7]. A study by Penel et al found that RIS comprise approximately 3% of all soft tissue sarcomas [8]. The first reported case occurred early in the 1920's, yet little is known about the molecular biology of this rare disease; consequently, no targeted therapy is available for RIS. A second primary malignancy typically recurs 10 years after the first malignancy and in some cases, the latency period can be as long as 20 years [9-11].However, there have been many RIS with a much shorter latent period [12]. Radiation induced cutaneous angiosarcomas typically have shorter latent periods than other types of RIS of the breast [13, 14].

Establishing an accurate diagnosis of RIS is critical before embarking on clinical treatment. Cahan et al suggests that to be classified as a RIS, (1) there must be evidence of an initial malignant tumor of a different kind other than the present sarcoma, (2) development of a second tumor, the sarcoma, in the irradiated field, (3), a prolonged latent period (typically > 4 years), and (4) histological evidence of a sarcoma [15-17].

We present a review of the literature classifying articles based on a hierarchal level of evidence [18] that addresses best available data for specific clinical questions. This review

critically evaluates the medical literature regarding the management of radiation induced sarcomas (RIS) of the breast.

**Methods**

Articles were obtained using a PubMed search with the keywords *radiation induced sarcoma of the breast, radiation induced angiosarcoma of the breast, second primary malignancy of the breast, angiosarcoma and breast,* and *radiotherapy angiosarcoma of the breast.* The search provided articles specific to RIS of the breast many of which were articles ranging from the years 1970 to 2010. Further articles were obtained by searching references found within these articles. A total of 115 references were analyzed in preparation for this review. Review articles that did not include original research were excluded from our search. Furthermore, included were articles dealing with clinical trials and retrospective cohort series or case reports of radiation induced soft tissue sarcomas. Excluded were studies exclusively of sarcomas of the bone; papers not specifically related to breast cancer were not included.

**What is the effect of radiation therapy dose for risk of primary breast cancer on RIS?**

Due to the rarity of this particular malignancy, risk factors for the development of RIS are difficult to elucidate. However, with increased survival rates for primary breast cancer patients, the incidence of RIS is increasing. Studies have revealed that breast cancer and non- Hodgkin lymphoma are the most common previous cancers leading to RIS [8, 19]. A study by Cozen et al found a significantly increased risk of developing an angiosarcoma for patients who have previously been diagnosed with breast cancer compared to those who have not [11]. Previous radiation has been considered an etiological factor for RIS since the first few cases were introduced [5, 20-23]. A study reported that breast cancer patients have a 5 fold increased risk of developing an angiosarcoma compared to a population without breast cancer [24]. A Slovenian

study revealed that breast cancer patients have a 33% higher risk of developing a second cancer than the rest of the population [25]. Radiation therapy as well as chemotherapy for breast cancer patients is believed to have increased the risk for RIS [26].

A dose-response effect was found between the amount of radiation received for treatment of breast cancer and the risk of developing a soft tissue sarcoma. However, a reduction in the amount of radiation was not found to reduce the risk of sarcomas, simply that women receiving radiation had a much higher risk of developing RIS than women only receiving surgical excision as their primary treatment for breast cancer [27, 28]. Karlsson et al reported that there is a direct dose relationship between radiation energy and risk of sarcoma up to a dosage of 150-200 Joules (J); after that point, the relationship was unclear [29]. However, a dose of 10 Gray (Gy) has typically been reported as a minimum total dose to induce RIS [30]. A study reported by Clarke et al revealed that women receiving radiation therapy had a 20% higher risk of developing a second primary malignancy compared to those women not receiving radiation therapy for treatment of primary breast cancer [31]. However, through years of study, the risk of developing a RIS is small compared to the overall potential for benefit for radiation therapy for treatment of a primary breast cancer [1, 32]. The levels of evidence for this data ranged from 3-5c; there were no prospective randomized trials on radiation risk.

**What are other possible etiological causes of RIS of the breast?**

Cases have been reported in which treatment for infiltrating ductal carcinoma has been followed by RIS [33]. It has also been suggested that there may a genetic etiology for RIS due to a BRCA-1 mutation causing increased sensitivity to radiation [34]. Other noted factors may be hereditary diseases such as Li –Fraumeni, the site of radiation from the initial tumor, and concomitant chemotherapy with alkylating agents which may increase the risk of developing a

secondary tumor [35]. On the contrary, a randomized study by Valagussa et al found that patients receiving chemotherapy for treatment of primary breast cancer did not have a higher risk of developing a second malignancy [37].

**How do RIS of the breast compare to primary sarcomas of the breast?**

When comparing RIS to primary sarcomas of the breast, both have a low incidence rate of less than 1%. In addition, RIS have a similar clinical presentation to primary sarcomas of the breast. Typically, a primary sarcoma presents itself as a large, firm mass within the breast without a prior history of breast cancer. However, RIS are slightly more difficult to identify by physical examination due to postradiotherapy changes [38]. Both types have a wide histopathologic subtype variety but the most frequently reported types of sarcomas are leiomyosarcomas, fibrous histiocytomas, liposarcomas, fibrosarcomas, and angiosarcomas (the most common histologic subtype of RIS) [29, 39, 40]. Primary and secondary sarcomas of the breast appear identical histologically [3, 20]  Most importantly, the imaging of primary sarcomas appears similar to those of RIS, making diagnosis difficult [41]. Figure 3 provides the histology of a radiation induced spindle cell sarcoma of the breast. The most common location for a RIS was on the chest wall [8].

A study revealed that radiation associated sarcomas have a much lower disease free survival rate than sporadic soft tissue sarcomas. In addition, there is much more concern about toxicity when dealing with treatment of RIS because of previous adjuvant therapy and/or previous surgery [42]. There is an increased risk for complications in these patients; therefore, there are fewer treatment options since the patient has already received the maximum safe dose of radiation therapy.

When looking at angiosarcomas, a variant of RIS [43], radiation induced angiosarcomas typically appear in cutaneous areas whereas sporadic angiosarcomas arise in the parenchyma [44]. Secondary angiosarcomas are more difficult to identify clinically because they present as skin thickening and discoloration therefore causing a delay in diagnosis [45, 46]. In addition, radiation induced angiosarcomas have a differential diagnosis including inflammatory breast carcinoma, erythema, edema of the breast or possibly mammary oedema, fibrous histiocytoma, or possibly an infectious etiology [44, 47-49]. The most common radiation induced angiosarcoma has been found to be haemangiosarcoma [11].The articles distinguishing RIS from primary sarcomas were classified as 3-5c.

A study by Kondeur et al portrayed the significance of KIT expression in RIS, expressing the possibility of a KIT inhibitor for treating RIS. Spontaneous sarcomas were not shown to express KIT as frequently as RIS, providing a distinguishing factor for RIS [73].

**How are RIS of the breast clinically detected and diagnosed?**

In cases of radiation induced angiosarcomas, skin changes are prevalent and can be highly indicative of disease. These changes appear as skin discoloration ranging from red to purple, elevated skin, and skin thickening [6, 14, 30, 44, 50-56]. Therefore, when performing a skin biopsy, the specimen should be taken from the darkest and most infiltrated area [57]. There may also be some evidence of bruising of the skin [58]. Moore et al suggested comparing all follow-up mammograms instead of the most recent one. In addition, this study noted the importance of paying close attention to images of the quadrant of the breast where skin changes have been noted by the patient [51]. RIS can be distinguished from Stewart-Treves syndrome, a swelling of the arm after radical mastectomy for breast cancer, by the occurrence of angiosarcoma in patients with lymphedematous extremities after radical mastectomy [59].

RIS can be identified using a fine needle aspiration (FNA) in rare cases. However, it is difficult to distinguish from recurrent carcinoma due to small sample volume, morphologic similarity to carcinoma cells, and paucity of vasoformative areas in the neoplasm [60]. FNA would not be expected to provide definitive information about histology architecture, rather would show cellular morphology based on cytological features. In most cases FNA may reveal inconclusive evidence, therefore, incisional biopsy is the preferred biopsy strategy [45, 47, 52, 61-63]. Importantly, mammograms may reveal false negative results, making MRI and incisional biopsies even more valuable when diagnosing RIS [64, 65]. Studies have reported that a mammogram may be negative after skin changes have been noticed [49, 54, 65, 66]. In addition, in cases of negative results, an excisional biopsy, including skin and subcutaneous tissue is preferred [6, 14, 55]. Levels of evidence for information regarding biopsies are based on levels 3b and 5c.

Advances in imaging techniques such as Magnetic Resonance Imaging (MRI) along with three dimensional reconstructions can help provide excellent preoperative planning of the extent of resection [67, 68]. MRI images have shown to reveal the spread of a tumor and can predict chest wall involvement [67]. MR imaging can also reveal the extent of the disease to the surgeon and because of preoperative knowledge, it can help prevent hemorrhagic complications [69]. MRI images of a patient with spindle cell sarcoma are shown in Figure 1.

The histopathologic features of RIS have typically been reported to consist of spindle shaped tumor cells, hemorrhagic tumor nodules, mitotic figures, and necrosis [33, 63, 70, 71]. Figure 3 provides an example of RIS with spindle cells. The most common sites of metastasis include the lungs and the lymph nodes [72]. It is important to note that the levels of evidence used for information on diagnosis came from levels 3-5c; no level 1 studies were found.

**What are the survival rates and which prognostic factors are important to consider?**

Recent studies have found a 5-year-survival rate of 27%-48% for RIS [4, 74]. Disease free survival rates were found to be 35% [6]. Skin lesions appear to be an important prognostic factor for survival rates. For radiation induced angiosarcoma, patients with multiple lesions on the skin had a 0% two year survival rate whereas patients with a single lesion had a 50% two year survival rate [2]. Median survival rates have been reported as 23 months for RIS patients [75].

Tumor size appears to be an important prognostic factor for survival in RIS. Tumors less than 2 cm had a median survival rate of 80 months while tumors that were larger than 5 cm had a median survival rate of only 20 months [68]. Blanchard et al reported that patients with a smaller mean tumor size (3.3 cm) had less local recurrence than patients with a mean larger sarcoma (7.9 cm) [16]. Local recurrence rates have been reported to be high with rates ranging from 50%-68% [4].

Tumor grade also plays an important role in the prognosis of RIS. De Smet et al reported that 80% of the secondary sarcomas were high-grade whereas only 40% of primary sarcomas are high-grade (grade 3). Most other cases of RIS are typically high grade as well [76]. Low grade tumors have been shown to have better outcomes in terms of disease free survival [75, 76]. Patients with a high grade tumor were also seen to have a high stage of disease and concurrently, a much lower 5 year survival rate of only of only 18%. While most RIS do consist of high grade tumors, there are cases where it may also be a low grade RIS [58]. The location of the tumor and the presence of positive lymph nodes are also significant when diagnosing RIS [35]. Many studies have noted negative lymph nodes in RIS patients [55, 56, 71, 77], underscoring that

sarcoma does not tend to metastasize via a lymphatic route. On this basis, no nodal evaluation procedure is recommended for the surgical treatment of RIS.

Brady et al revealed three important factors that have an unfavorable result on tumor mortality: presentation with metastatic disease, incomplete or no operative resection, and tumor size of at least 5 cm [78]. Levels of evidence for the data in these articles ranged from 3-5c which consists of cohort studies, case control studies, or case reports.

**What is the optimal surgical treatment for RIS?**

Unfortunately, the medical literature lacks certainty about successful treatment options for RIS. However, certain treatments have been shown to be more effective than others. Many studies demonstrated that neither chemotherapy nor radiation therapy alone is sufficient in the treatment of RIS [16, 68, 79, 80]. Therefore, surgery is a crucial treatment factor [81]. The most appropriate management is wide local excision with negative surgical margins. Various studies have discussed the importance of negative margins when performing a resection for RIS. Positive margins were shown to significantly increase the risk of local recurrence [26, 68, 82]. Studies have conveyed that traditionally, 2-4 cm negative margins are necessary for proper disease clearance [53, 83, 84], although other studies have used 1 cm with successful local control [66]. An aggressive surgical approach is crucial to decrease the risk of recurrence; one study suggested that for proper margin control, the surgeon should extirpate one plane beyond the anatomical plane of known disease [4]. In addition, for tumors that arise in previously irradiated fields or have extensive disease infiltration, it is important to perform a mastectomy, or in some cases, an extended radical mastectomy with *en bloc* chest wall excision[68]. Souba et al revealed good outcomes with complete excision and a chest wall resection for multiple RIS patients [85]. Despite low disease free survival for chest wall resections, it is justified based on

low postoperative morbidity and lack of other treatment options [86]. Figure 2 illustrates a patient with spindle cell sarcoma of the chest wall who required radical surgery due to the extent of infiltration beyond the breast into the chest wall, necessitating a chest wall resection.

A few studies discussed the importance of a total mastectomy as soon as a diagnosis is made in all cases of radiation induced angiosarcomas [50, 77, 81, 87, 88]. Colville et al recommended complete mastectomy with a 5cm margin [89]. Turner et al also excised under the pectoral muscle and achieved nodal clearance in addition to mastectomy [90]. However, it has been noted that axillary dissection should be avoided to prevent the potential treatment related morbidity of lymphedema [68].

Although surgery is the most effective treatment available for RIS, surgery alone has often proven to be lacking in terms of overall survival and local recurrence rates [68, 91]. The hierarchal levels of evidence for these studies ranged from 3-5 with most articles being classified as 5c, case series or case reports. No prospective randomized trials of margin width were available in the published literature. This underscores the need for a multidisciplinary approach to the management of RIS so that best clinical judgment may be applied for each case of RIS.

**What is the current role of adjuvant/neoadjuvant therapy for treating RIS?**

Many studies have revealed poor outcomes in terms of survival and local recurrence rates when combining surgery with standard adjuvant therapy [26, 78, 79, 92]. Lagrange et al reported no difference in survival rates between patients treated with surgery versus those treated with surgery plus chemotherapy [75]. However, other studies have reported that following resection with widely negative margins, adjuvant therapy may prove to be beneficial. [42, 68, 77, 86, 91, 93, 94]. Barrow et al reported a favorable result for combining chemotherapy with radiation after surgery [68]. Angiosarcomas have also been shown to respond to the combination of radiation

therapy and surgery [62, 94]. A study by Rosen et al revealed that adjuvant chemotherapy had beneficial results on disease free survival rates for patients who received adjuvant therapy versus those who did not. However, this result was only seen with a Type III (high grade) aggressive angiosarcoma and not with Type I or II (low grade and intermediate grade, respectively) Patients with a type I tumor who received adjuvant chemotherapy had a 20% recurrence versus 27% recurrence in those patients not receiving therapy. With Type III tumors, 71% of patients receiving radiation had recurrence as opposed to 100% of the patients not receiving radiation treatment. [93].

Kuten et al discussed the value of giving patients CYVADIC (cyclophosphamide, vincristine, adriamycin, DTIC) therapy. Patients were either given surgery with this combination chemotherapy or just the chemotherapy alone. Unfortunately, every patient died within 6-36 months from the time of their initial diagnosis leading them to conclude that this regimen is ineffective [79]. In addition, Brady et al revealed no difference in 5 year survival rates between patients receiving chemotherapy as part of their treatment and patients not receiving chemotherapy [78].

However, chemotherapy combining anthracyclins, dacarbazine, and ifosfamide has been shown to be effective on RIS patients [95]. In addition, Yap et al revealed that chemotherapy drugs such as methotrexate, 5-FU, and adriamycin combined with DTIC may give a favorable response for lymphangiosarcoma [96]. Another study reported great sensitivity of radiation induced angiosarcomas to the chemotherapeutic drug docetaxel [97]. Paclitaxel also showed improved results with angiosarcomas [98, 99].

With adjuvant therapy, histologic examination of surgical pathology specimens is more straightforward and the design of postoperative radiation therapy is more common compared to

neoadjuvant radiation therapy. However, post-operative radiation therapy usually results in greater toxicities [100]. Additionally, it is believed to be less effective on RIS because of fibrotic changes, resulting in an inadequate blood supply [79].

An article by Quadros et al reports a positive outcome for neoadjuvant therapy followed by surgery as a more promising way to treat RIS [74]. However, only a single article was identified in our systematic literature search discussing outcomes of neoadjuvant chemotherapy on RIS. With neoadjuvant therapy, the tumor burden may be reduced such that surgical excision is facilitated resulting in potentially less morbidity. However, complications with tissue quality may result.

With so little data on treatment for RIS, studies on primary sarcomas may be a close alternative. Okuno et al described the prevalence of the chemotherapy drugs doxorubicin and ifosfamide in treating advanced sarcomas. A few randomized trials have been performed on patients with advanced soft tissue sarcomas. Adriamycin has found to give a 25% response rate which does not differ significantly from epiadriamycin which has an 18% response rate [101]. Additionally, a prospective randomized study by Santoro et al revealed an overall response rate of 24% to CYVADIC and doxorubicin plus ifosfamide. However, doxorubicin was considered the standard treatment as this large phase II trial could not confirm superiority of a combination treatment [102, 103]. Paclitaxel has also shown to be effective when treating advanced sarcomas [104-106]. . Okuno et al also reviewed new progress and studies on chemotherapy in the treatment of advanced soft tissue sarcomas [107]. Further studies may ultimately reveal new agents capable of eliciting a durable response for patients with RIS.

However, the overall role of chemotherapy in addition to surgery remains to be determined based on future clinical research studies. There is insufficient evidence concluding

whether adjuvant or neoadjuvant therapy provides significant benefits over surgery alone. With the development of novel chemotherapeutic agents, a combined approach may ultimately increase the chance of survival for RIS [4, 107, 108]. The role of adjuvant or neoadjuvant chemotherapy remains ambiguous with most articles possessing only levels 3-5c in our hierarchal levels of evidence classification. No level 1 or 2 studies were identified.

**What is the role of radiation therapy in the treatment of RIS?**

The literature also provides data on alternative and experimental options as an attempt to further treat RIS. A few studies have discussed the attempt at salvage therapy using radiation and hyperthermia for RIS patients that have provided favorable results [109, 110]. In addition, Feigenberg et al reported that hyperfractionated radiotherapy has been successful in treating radiation induced angiosarcomas [94]. A recent study by Palta revealed a similar result by giving hyperfractionated and accelerated radiation doses to patients with radiation induced angiosarcomas. An overall survival rate of 86% at 5 years for 14 patients was found with this new method [111]. Therefore, successful cases of a multi-modal approach are emerging, leading us to believe that more favorable outcomes are possible with continued research in the treatment of RIS.

Notably, radiation therapy has less effect on RIS than chemotherapy due to tolerance of radiation dosage from previous treatment [112, 113]. In addition, radiation therapy for RIS has been associated with significant side effects [64]. Data in support of using radiation to treat RIS was based on levels 3-5c in the hierarchal levels of evidence.

**Discussion**

Radiation induced sarcomas typically appear after a prolonged latency period after the treatment of breast cancer (usually around 11-14 years after radiation)[4]. While RIS of the

breast has a low occurrence rate, more breast cancer survivors may increase the prevalence of this disease. Studies have successfully found an association between radiation therapy used to treat breast cancer and the incidence of RIS [27, 29, 114].

Unfortunately, there is still much controversy as to the optimal management of this rare, aggressive disease [68, 80]. RIS are treated similarly to primary sarcomas of the breast [38]. Currently, it has been established that surgery is crucial to help eradicate a RIS [26]. An aggressive resection with widely negative margins is necessary for all non-metastatic patients [4, 68]. In addition, chest wall excision may be required if the tumor infiltrates beyond the breast into the chest wall [68].

Low survival rates have underscored the need for improved therapy options for the treatment of RIS. Adverse prognostic factors suggesting the need for adjuvant therapy include tumor size, grade, and histologic type. In addition, in certain cases, complete resection may not be possible due to extensive infiltration [26]. Therefore, some cases may warrant the need for neoadjuvant or adjuvant therapy. Our systematic review highlights the uncertainty of the effectiveness of adjuvant or neoadjuvant chemotherapy. No prospective randomized controlled trials of systemic therapy for RIS were identified due to the rarity of this disease. This leads us to conclude that the decision to consider adjuvant therapy in addition to surgery should be individualized and a treatment plan should be formed by a dedicated multidisciplinary team. Clearly, additional research needs to be performed to determine the efficacy of radiation and chemotherapy in addition to surgery.

With the emergence of a growing number of breast cancer survivors and the aggressiveness of RIS, it is imperative to improve our understanding of the biology and treatment of RIS. Proper follow up care is crucial for achieving optimal results. One study

suggested the importance of long term surveillance of skin changes in the irradiated field as these can often be the site of RIS [115]. Earlier detection may lead to better results allowing complete surgical resection with negative margins. In addition, there is a lower recurrence rate with small tumor size [16]. Aggressive radical surgery is crucial with widely negative margins. Lastly, adjuvant radiation or chemotherapy before or after surgery are options that may yield improved outcomes and are worthy of investigation via clinical trials or registry studies.

In the absence of randomized clinical trials, it is impossible to identify conclusive evidence for the optimal management of RIS. Table 1 provides our systematic review of the medical literature that was analyzed for this paper. Much of the data rely on case reports and retrospective, single institutional cohort studies which fall low on the hierarchal levels of evidence, limiting reaching a definitive conclusion on the best practices in the treatment of this rare, aggressive disease. RIS is a challenging and often lethal malignancy; however, some progress has been made in recent years that can serve as a solid foundation for future research studies. Over time, RIS patients may experience better outcomes due to more established treatment plans. Our systematic review underscores the need for prospective, randomized trials, registry studies and well designed retrospective cohort studies to guide best clinical management for RIS.

**Table 1: Levels of Evidence**

| First Author | Year | Level of Evidence | Type of Study (n= for RIS after breast cancer) | Primary Endpoint |
|---|---|---|---|---|
| Velaj (1) | 1987 | 5c | Radiographic Review (n=1) | Case report and review of the literature. |
| Erel | 2010 | 3b | Retrospective review (n=25) | Overall survival and local recurrence rate. |
| Olcina | 2008 | 5c | Case report (n=1) | Case report and review of the literature. |
| Chahin | 2001 | 5c | Case report (n=1) | Case report and review of the literature. |
| Penel | 2008 | 3a | Prospective cohort study (n=9) | Prognostic factors and risk factors associated with soft tissue sarcomas. |
| Pendlebury | 1995 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Blanchard | 2002 | 3b | Retrospective Review (n=34) | Effect of tumor size of RIS on survival. |
| West | 2005 | 3a | Cohort Study (n=4, Orange, CA registry, n= 9 French registry ,n= 21 Dutch registry) | Prevalence of angiosarcoma following breast conserving surgery. |
| Tahir | 2006 | 5c | Case report (n=1) | Case report and review of the literature. |
| Moore | 2008 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Hanasono | 2005 | 5c | Case report (n=1) | Case report and review of the literature. |
| Rao | 2001 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Esler-Brauer | 2007 | 5c | Case report (n=1) | Case report and review of the literature. |
| Nakamura | 2007 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Soldic | 2009 | 5b | Case Report (n=1) | Case report and review of the literature. |
| Biswas | 2009 | 3b | Retrospective Review (n=8) | Overall survival and recurrence free survival. |
| Mills | 2001 | 5c | Case report (n=2) | Case report and review of the literature. |
| Barrow | 1999 | 3b | Retrospective | Clinicopathologic risk |

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| | | | review (n=59) | factors, adjuvant therapies, overall survival and disease free survival. |
| McGowan | 2000 | 3b | Retrospective Review (n=78) | Prognostic factors and risk factors; overall and relapse free survival. |
| Karlsson | 1996 | 4 | Case control study (n=19) | Association between arm lymphedema, radiotherapy, and RIS. |
| Karlsson | 1998 | 4 | Case control Study (n=116) | Effect of lymphedema and radiotherapy dose on development of RIS. |
| Huang | 2001 | 3b | Retrospective cohort study (n=54) | Risk factors for RIS. |
| Gladdy | 2010 | 3a | Matched Cohort analysis (n=130) | Prognostic factors in RIS; outcome of RIS versus sporadic soft tissue sarcoma. |
| Kunkel | 2008 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Virtanen | 2007 | 3a | Cohort Study (n=19) | Risk factors for RIS. |
| Thijssens | 2005 | 3b | Retrospective Review (n=27) | Disease free and overall survival outcomes; local recurrence rates. |
| Rubino | 2005 | 4 | Case control study (n=14 ) | Risk factor of radiation dose for RIS. |
| Holt | 2006 | 5b | Prospective cohort with mixed disease types (n=10) | Prevalence of multifocality of RIS. |
| Yap | 2002 | 3a | Prospective registry study (n=87) | Risk factor of radiotherapy in development of RIS. |
| Quadros | 2006 | 5c | Case Report (n=1) | Case report and review of the literature. |
| De Smet | 2008 | 3b | Retrospective cohort with mixed disease types (n=23) | Overall survival, prognostic factors, and local recurrence rates. |
| Kuten | 1985 | 5c | Case Report (n=7) | Case report and review of the literature. |
| Khan | 2009 | 5c | Case Report (n=1) | Case report and review of the literature. . |
| Cha | 2004 | 3a | Prospective Review (n=123) | Overall survival and prognostic markers in RIS |
| Plotti | 2006 | 5c | Case Report (n=1) | Case report and review of the |

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| | | | | literature. |
| Marchal | 1998 | 3b | Retrospective Review (n=9) | Overall survival and incidence of RIS. |
| Bjerkehagen | 2008 | 3b | Review of database patients (n=90) | Overall survival and prognostic factors in RIS. |
| Brenin | 1998 | 5c | Case report (n=1) | Case report and review of the literature. |
| Brady | 1992 | 3b | Review of database patients (n=160) | Overall survival and prognostic factors in RIS. |
| Chapelier | 1997 | 3b | Retrospective Review (n=15) | Outcomes of radical resection of RIS of the chest wall. |
| Feigenberg | 2002 | 5c | Case Report (n=3) | Case report and review of the literature. |
| Schulz | 1999 | 5c | Case report (n=3) | Case report and review of the literature. |
| Givens | 1999 | 5c | Clinical review (n=85) | Analysis of prognostic factors for RIS. |
| Okuno | 1998 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Neuhaus | 2008 | 3b | Retrospective Review (n=67) | Local relapse rates and prognostic factors in RIS. |
| Kirova | 2004 | 3b | Review of records (n=35) | Overall survival in RIS. |
| Mano | 2006 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Perez-Ruiz | 2009 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Gambini | 2009 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Palta | 2010 | 3b | Retrospective Review (n=14) | Effect of hyperfractionated and accelerated radiation therapy on RIS. |
| deGiorgi | 2009 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Travis | 1976 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Hardy | 1978 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Tsuneyoshi | 1979 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Chen | 1979 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Pierce | 1992 | 3a | Prospective | Risks of radiation therapy for |

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| | | | Review(n=3) | primary breast cancer on developing RIS. |
| Sener | 2001 | 3b | Retrospective Review (n=5) | Latency periods and histologic features of RIS. |
| Autio | 1999 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Bolin | 1996 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Deutsch | 1998 | 5c | Case Report (n=1) | Case report and review of the literature. |
| Lamblin | 2001 | 5c | Case reports (n=4) | Case report and review of the literature. |
| Williams | 1999 | 5c | Case report (n=1) | Case report and review of the literature. |
| Fant | 2003 | 5c | Case report (n=1) | Case report and review of the literature. |
| Mermershtain | 2002 | 5c | Case report (n=1) | Case report and review of the literature. |
| deBree | 2002 | 5c | Case report (n=1) | Case report and review of the literature. |
| Adhikari | 2002 | 5c | Case report (n=1) | Case report and review of the literature. |
| Colville | 2000 | 5c | Case report (n=1) | Case report and review of the literature. |
| Georgiannos | 2003 | 3b | Retrospective Review (n=4) | Incidence and clinicopathologic features of RIS. |
| Cozen | 1999 | 4 | Case Control Study (n=48) | Risks of developing angiosarcoma after treatment for primary breast cancer. |
| Majeski | 2000 | 5c | Case report (n=1) | Case report and review of the literature. |
| Strobbe | 1998 | 3b | Retrospective review (n=21) | Latency periods, overall survival, and clinicopathologic features of RIS. |
| Billings | 2004 | 3b | Retrospective review (n=27) | Histologic and clinical features of angiosarcoma after breast cancer therapy. |
| Cafiero | 1998 | 5b | Case Reports (n=2) | Case report and review of the literature. |
| Stokkel | 1991 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Marchant | 1997 | 5c | Case report(n=1) | Case report and review of the literature. |
| Buatti | 1994 | 5c | Case report (n=1) | Case report and review of the |

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| Fineberg | 1994 | 3b | Retrospective Review (n=3) | Comparing angiosarcoma to atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. |
| Fodor | 2006 | 3b | Retrospective review (n=8) | Latency periods, overall survival, and clinicopathologic features of RIS. |
| Gherardi | | 5c | Case report (n=3) | Case report and review of the literature. |
| Badwe | 1991 | 5c | Case report (n=1) | Case report and review of the literature. |
| Moskaluk | 1992 | 5c | Case report (n=1) | Case report and review of the literature. |
| Edeiken | 1992 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Zucali | 1994 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Sessions | 1992 | 5c | Case report (n=1) | Case report and review of the literature. |
| Roukema | 1991 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Turner | 1991 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Otis | 1986 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Lo | 1984 | 5c | Case report (n=1) | Case report and review of the literature. |
| Benda | 1987 | 5c | Case report(n=1) | Case report and review of the literature. |
| Hamels | 1981 | 5c | Case report (n=1) | Case report and review of the literature. |
| Shaikh | 1988 | 5c | Case report (n=1) | Case report and review of the literature. |
| Rubin | 1990 | 5c | Case report (n=1) | Case report and review of the literature. |
| Del Mastro | 1994 | 5c | Case report (n=1) | Case report and review of the literature. |
| Cwikiel | 1997 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Roncadin | 1998 | 5c | Case report (n=1) | Case report and review of the literature. |
| De Bree | 2002 | 5c | Case report (n=1) | Case report and review of the literature. |

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| Parker | 2003 | 5c | Case report (n=1) | Case report and review of the literature. |
| Amendola | 1989 | 3b | Retrospective review (n=1) | Effect of radiation therapy for primary breast cancer on RIS. |
| Lagrange | 2000 | 3b | Retrospective review (n=33) | Overall survival rates and treatment plans. |
| Taat | 1992 | 5c | Case report (n=1) | Case report and review of the literature. |
| Weber | 1995 | 5c | Case reports (n=3) | Case report and review of the literature. |
| Iwasaki | 1978 | 5c | Case report (n=1) | Case report and review of the literature. |
| Arbabi | 1982 | 5c | Case report (n=1) | Case report and review of the literature. |
| Davidson | 1986 | 3b | Retrospective review (n=6) | Effect of radiation dosage on latent period; common histological types. |
| Souba | 1986 | 3b | Case reports (n=10) | Case report and review of the literature. |
| Wiklund | 1991 | 3b | Retrospective Review (n=7) | Impact of radical surgery on RIS of the breast. |
| Kim | 1978 | 3b | Retrospective Review (n=10) | Latency periods and diagnostic criteria for RIS. |
| Murray | 1999 | 3b | Retrospective review (n=3) | Risk factor of radiotherapy in development of RIS. |
| Sheppard | 2001 | 3b | Retrospective review (n=17) | Cross sectional imaging findings in patients with RIS. |
| Hatfield | 1970 | 5c | Case series (n=5) | Case report and review of the literature. |
| Borman | 1997 | 5c | Case report (n=1) | Case report and review of the literature. |
| Vesoulis | 2000 | 5c | Case report (n=1) | Case report and review of the literature. |
| Kurtz | 1988 | 3b | Retrospective review (n=2) | Risk of contralateral breast cancer and sarcoma after breast cancer therapy. |
| Inoue | 2000 | 3b | Retrospective review (n=18) | Clincopathologic features of RIS of the breast. |
| Komdeur | 2003 | 3b | Translational research study (n=3) | Assessment of KIT as a potential target. |
| Mills | 2001 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Tarkkanen | 2001 | 3b | Translational research study | Comparative genomic hybridization of RIS. |

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| | | | (n=10) | |
| Schwarz | 1995 | 3b | Retrospective review(n=7) | Risk of radiation therapy on developing RIS. |
| Moe | 2007 | 5c | Case report (n=1) | Case report and review of the literature. |
| Volk | 1997 | 3b | Retrospective cohort study (n=108) | Risk of radiation therapy after breast cancer on developing RIS. |
| Hunter | 1985 | 5c | Case reports (n=2) | Case report and review of the literature. |
| Tomasini | 2004 | 5c | Case report (n=1) | Case report and review of the literature. |
| Pitcher | 1993 | 3b | Retrospective review (n=13) | Clinicopathologic features of RIS. |

Figure 1

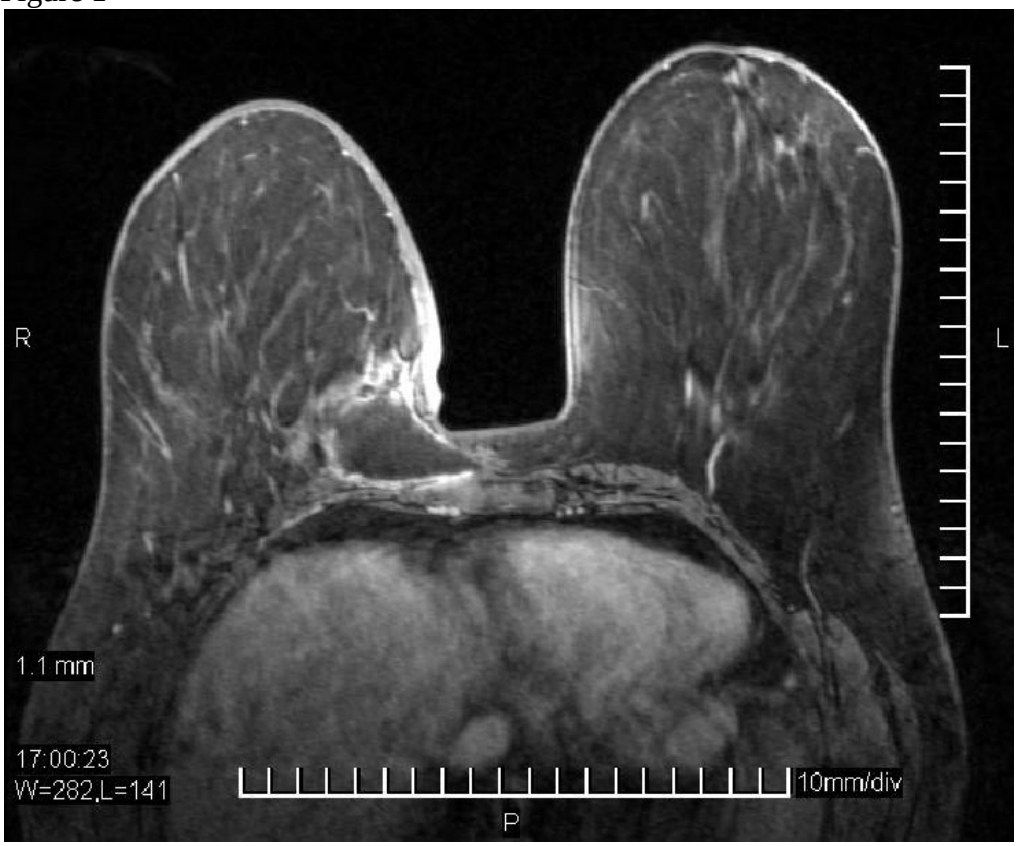



Figure 2a

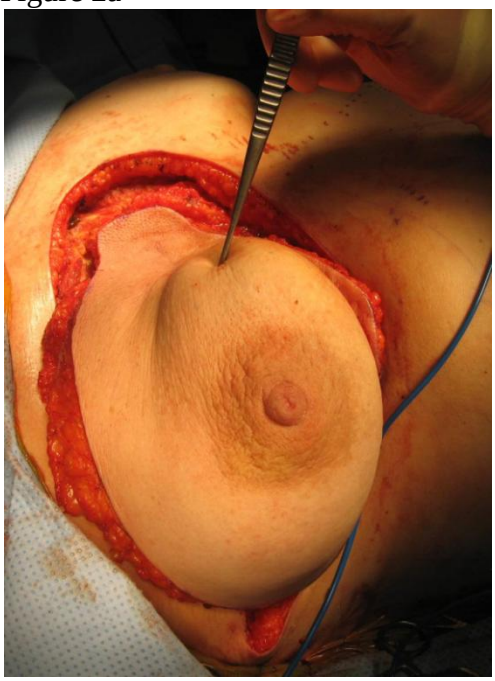


Figure 2b

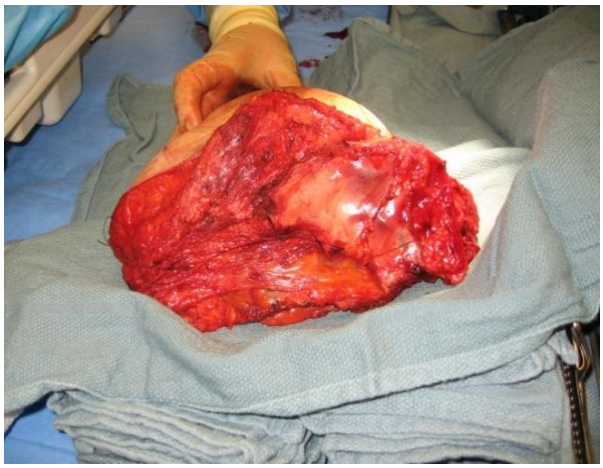


Figure 2c

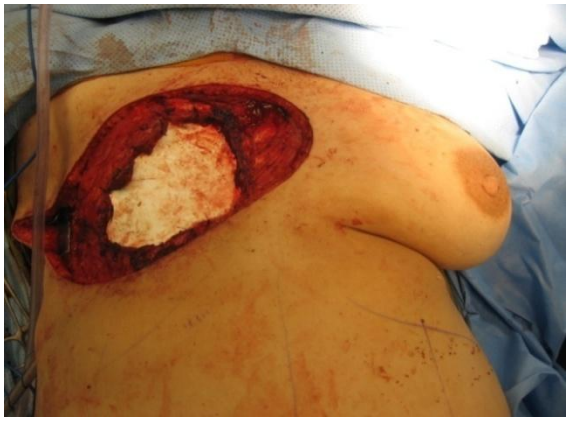
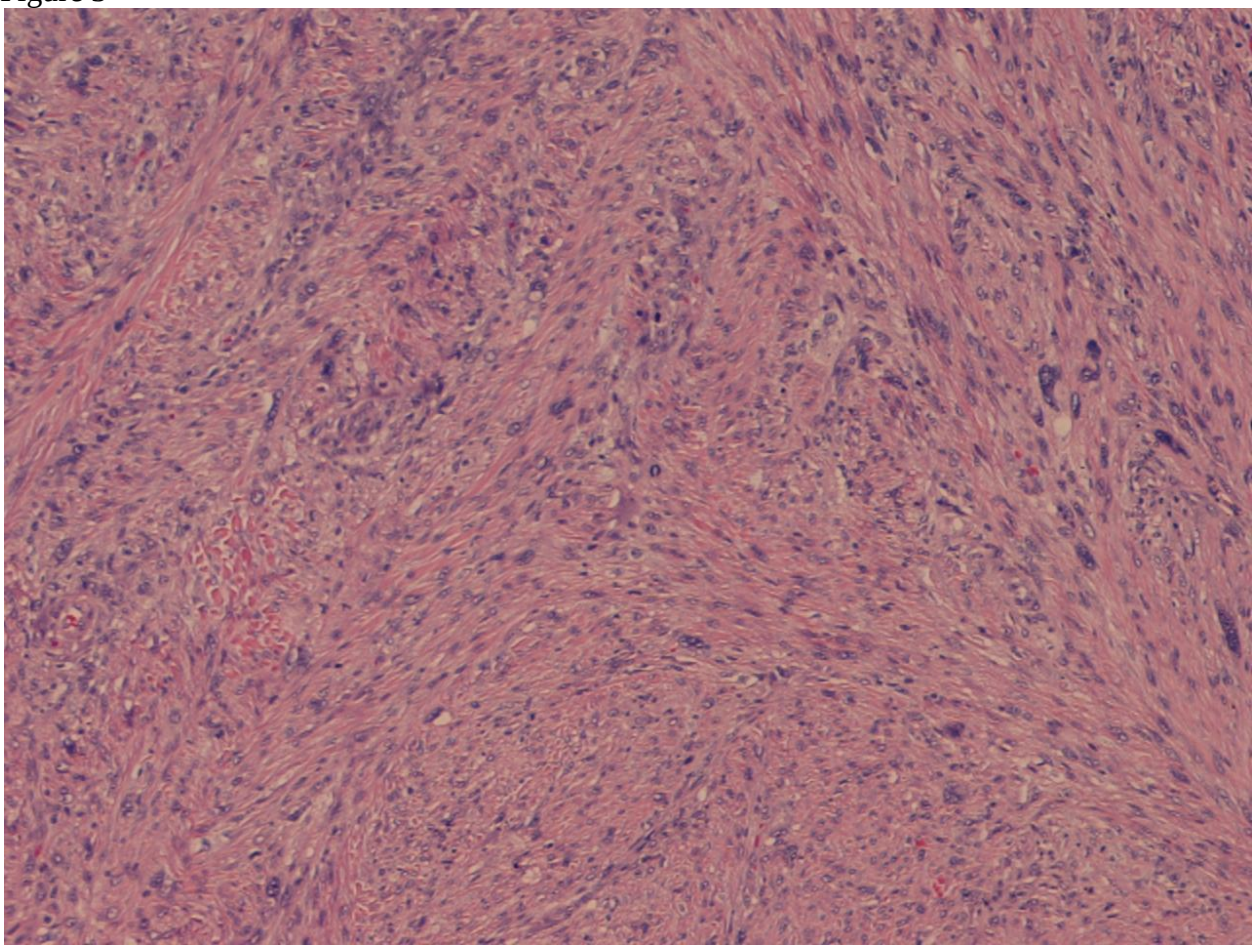


Figure 3



## Figure Legend

**Figure 1:** Coronal MRI of the patient with RIS. There appears as though there may be some tumor involvement with the chest wall.

**Figure 2: (a)** Intraoperative view of the mastectomy specimen prior to excision. Forceps are used to illustrate that the RIS is externally visible due to its large size and displacement of normal breast tissue. **(b)** Posterior view of the mastectomy specimen. The RIS is protruding from the breast parenchyma and required the complete removal of the adjoining chest wall. **(c)** Lumpectomy cavity following radical mastectomy. A significant portion of the chest wall was removed to ensure negative margins.

**Figure 3:** Striking low power appearance due to cellularity, vague whorled pattern and marked nuclear atypia.

References


1. Yap, J., et al., *Sarcoma as a second malignancy after treatment for breast cancer.* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1231-7.
2. Fodor, J., et al., *Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature.* J Am Acad Dermatol, 2006. **54**(3): p. 499-504.
3. Velaj, R.H. and S.A. DeLuca, *Radiation-induced sarcoma.* Am Fam Physician, 1987. **36**(5): p. 129-30.
4. Erel, E., et al., *Management of radiation-induced sarcomas in a tertiary referral centre: A review of 25 cases.* Breast.
5. Pierce, S.M., et al., *Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer.* Int J Radiat Oncol Biol Phys, 1992. **23**(5): p. 915-23.
6. Strobbe, L.J., et al., *Angiosarcoma of the breast after conservation therapy for invasive cancer, the incidence and outcome. An unforseen sequela.* Breast Cancer Res Treat, 1998. **47**(2): p. 101-9.
7. Zucali, R., et al., *Soft tissue sarcoma of the breast after conservative surgery and irradiation for early mammary cancer.* Radiother Oncol, 1994. **30**(3): p. 271-3.
8. Penel, N., et al., *Frequency of certain established risk factors in soft tissue sarcomas in adults: a prospective descriptive study of 658 cases.* Sarcoma, 2008. **2008**: p. 459386.
9. Olcina, M., et al., *Radiation-Induced Leiomyosarcoma after Breast Cancer Treatment and TRAM Flap Reconstruction.* Sarcoma, 2008. **2008**: p. 456950.
10. Travis, E.L., et al., *Unusual postirradiation sarcoma of chest wall.* Cancer, 1976. **38**(6): p. 2269-73.
11. Cozen, W., et al., *The risk of angiosarcoma following primary breast cancer.* Br J Cancer, 1999. **81**(3): p. 532-6.
12. Chahin, F., et al., *Angiosarcoma of the breast following breast preservation therapy and local radiation therapy for breast cancer.* Breast J, 2001. **7**(2): p. 120-3.
13. Fineberg, S. and P.P. Rosen, *Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma.* Am J Clin Pathol, 1994. **102**(6): p. 757-63.
14. Sessions, S.C. and R.D. Smink, Jr., *Cutaneous angiosarcoma of the breast after segmental mastectomy and radiation therapy.* Arch Surg, 1992. **127**(11): p. 1362-3.
15. Pendlebury, S.C., M. Bilous, and A.O. Langlands, *Sarcomas following radiation therapy for breast cancer: a report of three cases and a review of the literature.* Int J Radiat Oncol Biol Phys, 1995. **31**(2): p. 405-10.
16. Blanchard, D.K., et al., *Radiation-induced breast sarcoma.* Am J Surg, 2002. **184**(4): p. 356-8.
17. Cahan, W.G., H.Q. Woodard, and et al., *Sarcoma arising in irradiated bone; report of 11 cases.* Cancer, 1948. **1**(1): p. 3-29.
18. Hadorn, D.C., et al., *Rating the quality of evidence for clinical practice guidelines.* J Clin Epidemiol, 1996. **49**(7): p. 749-54.
19. Laskin, W.B., T.A. Silverman, and F.M. Enzinger, *Postradiation soft tissue sarcomas. An analysis of 53 cases.* Cancer, 1988. **62**(11): p. 2330-40.
20. Chen, K.T., K.D. Hoffman, and E.J. Hendricks, *Angiosarcoma following therapeutic irradiation.* Cancer, 1979. **44**(6): p. 2044-8.

21. Hardy, T.J., et al., *Postirradiation sarcoma (malignant fibrous histiocytoma) of axilla.* Cancer, 1978. **42**(1): p. 118-24.
22. Tsuneyoshi, M. and M. Enjoji, *Postirradiation sarcoma (malignant fibrous histiocytoma) following breast carcinoma: an ultrastructural study of a case.* Cancer, 1980. **45**(6): p. 1419-23.
23. Edeiken, S., et al., *Angiosarcoma after tylectomy and radiation therapy for carcinoma of the breast.* Cancer, 1992. **70**(3): p. 644-7.
24. Virtanen, A., E. Pukkala, and A. Auvinen, *Angiosarcoma after radiotherapy: a cohort study of 332,163 Finnish cancer patients.* Br J Cancer, 2007. **97**(1): p. 115-7.
25. Volk, N. and V. Pompe-Kirn, *Second primary cancers in breast cancer patients in Slovenia.* Cancer Causes Control, 1997. **8**(5): p. 764-70.
26. Thijssens, K.M., et al., *Radiation-induced sarcoma: a challenge for the surgeon.* Ann Surg Oncol, 2005. **12**(3): p. 237-45.
27. Rubino, C., et al., *Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment.* Breast Cancer Res Treat, 2005. **89**(3): p. 277-88.
28. Holt, G.E., et al., *Multifocality and multifocal postradiation sarcomas.* Clin Orthop Relat Res, 2006. **450**: p. 67-75.
29. Karlsson, P., et al., *Soft tissue sarcoma after treatment for breast cancer--a Swedish population-based study.* Eur J Cancer, 1998. **34**(13): p. 2068-75.
30. Tahir, M., et al., *Radiation induced angiosarcoma a sequela of radiotherapy for breast cancer following conservative surgery.* Int Semin Surg Oncol, 2006. **3**: p. 26.
31. Clarke, M., et al., *Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials.* Lancet, 2005. **366**(9503): p. 2087-106.
32. Fisher, B. and S.J. Anderson, *The breast cancer alternative hypothesis: is there evidence to justify replacing it?* J Clin Oncol. **28**(3): p. 366-74.
33. Stokkel, M.P. and H.L. Peterse, *Angiosarcoma of the breast after lumpectomy and radiation therapy for adenocarcinoma.* Cancer, 1992. **69**(12): p. 2965-8.
34. de Bree, E., et al., *Bilateral angiosarcoma of the breast after conservative treatment of bilateral invasive carcinoma: genetic predisposition?* Eur J Surg Oncol, 2002. **28**(4): p. 392-5.
35. De Smet, S., et al., *Radiation-induced sarcoma: analysis of 46 cases.* Acta Chir Belg, 2008. **108**(5): p. 574-9.
36. Roncadin, M., et al., *Breast angiosarcoma after conservative surgery, radiotherapy and prosthesis implant.* Acta Oncol, 1998. **37**(2): p. 209-11.
37. Valagussa, P., G. Tancini, and G. Bonadonna, *Second malignancies after CMF for resectable breast cancer.* J Clin Oncol, 1987. **5**(8): p. 1138-42.
38. Zelek, L., et al., *Prognostic factors in primary breast sarcomas: a series of patients with long-term follow-up.* J Clin Oncol, 2003. **21**(13): p. 2583-8.
39. Karlsson, P., et al., *Soft tissue sarcoma after treatment for breast cancer.* Radiother Oncol, 1996. **38**(1): p. 25-31.
40. Huang, J., *Increased Risk of Soft Tissue Sarcoma after Radiotherapy in Women with Breast Carcinoma.* Cancer, 2001. **92**(1): p. 9.
41. Sheppard, D.G. and H.I. Libshitz, *Post-radiation sarcomas: a review of the clinical and imaging features in 63 cases.* Clin Radiol, 2001. **56**(1): p. 22-9.

42. Gladdy, R.A., et al., *Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas?* J Clin Oncol. **28**(12): p. 2064-9.
43. Kunkel, T., et al., *Recurrence of secondary angiosarcoma in a patient with post-radiated breast for breast cancer.* Arch Gynecol Obstet, 2008. **278**(5): p. 497-501.
44. Bolin, D.J. and G.M. Lukas, *Low-grade dermal angiosarcoma of the breast following radiotherapy.* Am Surg, 1996. **62**(8): p. 668-72.
45. Soldic, Z., et al., *Parenchymal post-irradiation angiosarcoma: a case report.* Acta Clin Croat, 2009. **48**(4): p. 433-7.
46. Sener, S.F., et al., *The spectrum of vascular lesions in the mammary skin, including angiosarcoma, after breast conservation treatment for breast cancer.* J Am Coll Surg, 2001. **193**(1): p. 22-8.
47. Lamblin, G., et al., *Angiosarcoma after conservative treatment and radiation therapy for adenocarcinoma of the breast.* Eur J Surg Oncol, 2001. **27**(2): p. 146-51.
48. Lucas, D.R., *Angiosarcoma, radiation-associated angiosarcoma, and atypical vascular lesion.* Arch Pathol Lab Med, 2009. **133**(11): p. 1804-9.
49. Mermershtain, W., et al., *Cutaneous angiosarcoma of breast after lumpectomy, axillary lymph node dissection, and radiotherapy for primary breast carcinoma: case report and review of the literature.* Am J Clin Oncol, 2002. **25**(6): p. 597-8.
50. West, J.G., et al., *Risk of angiosarcoma following breast conservation: a clinical alert.* Breast J, 2005. **11**(2): p. 115-23.
51. Moore, A., et al., *Secondary angiosarcoma of the breast: can imaging findings aid in the diagnosis?* Breast J, 2008. **14**(3): p. 293-8.
52. Hanasono, M.M., et al., *Radiation-induced angiosarcoma after mastectomy and TRAM flap breast reconstruction.* Ann Plast Surg, 2005. **54**(2): p. 211-4.
53. Rao, J., et al., *Cutaneous angiosarcoma as a delayed complication of radiation therapy for carcinoma of the breast.* J Am Acad Dermatol, 2003. **49**(3): p. 532-8.
54. Deutsch, M. and M.M. Rosenstein, *Angiosarcoma of the breast mimicking radiation dermatitis arising after lumpectomy and breast irradiation: a case report.* Am J Clin Oncol, 1998. **21**(6): p. 608-9.
55. Majeski, J., R.M. Austin, and R.H. Fitzgerald, *Cutaneous angiosarcoma in an irradiated breast after breast conservation therapy for cancer: association with chronic breast lymphedema.* J Surg Oncol, 2000. **74**(3): p. 208-12; discussion 212-3.
56. Roukema, J.A., et al., *Angiosarcoma of the irradiated breast: a new problem after breast conserving therapy?* Neth J Surg, 1991. **43**(4): p. 114-6.
57. Autio, P. and A.L. Kariniemi, *Angiosarcoma. A rare secondary malignancy after breast cancer treatment.* Eur J Dermatol, 1999. **9**(2): p. 118-21.
58. Georgiannos, S.N. and M. Sheaff, *Angiosarcoma of the breast: a 30 year perspective with an optimistic outlook.* Br J Plast Surg, 2003. **56**(2): p. 129-34.
59. Stewart, F.W. and N. Treves, *Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica.* Cancer, 1948. **1**(1): p. 64-81.
60. Vesoulis, Z. and C. Cunliffe, *Fine-needle aspiration biopsy of postradiation epithelioid angiosarcoma of breast.* Diagn Cytopathol, 2000. **22**(3): p. 172-5.
61. Esler-Brauer, L., W. Jaggernauth, and N.C. Zeitouni, *Angiosarcoma developing after conservative treatment for breast carcinoma: case report with review of the current literature.* Dermatol Surg, 2007. **33**(6): p. 749-55.

62. Nakamura, R., et al., *Angiosarcoma arising in the breast following breast-conserving surgery with radiation for breast carcinoma.* Breast Cancer, 2007. **14**(2): p. 245-9.
63. Gherardi, G., et al., *Angiosarcoma after breast-conserving therapy: fine-needle aspiration biopsy, immunocytochemistry, and clinicopathologic correlates.* Cancer, 2005. **105**(3): p. 145-51.
64. Biswas, T., et al., *Angiosarcoma of the breast: a rare clinicopathological entity.* Am J Clin Oncol, 2009. **32**(6): p. 582-6.
65. Williams, E.V., et al., *Angiosarcoma of the breast following radiation therapy.* Eur J Surg Oncol, 1999. **25**(2): p. 221-2.
66. Fant, J., et al., *Angiosarcoma of the breast: mammographic, clinical, and pathologic correlation.* Breast J, 2003. **9**(3): p. 252-3.
67. Mills, T.D., et al., *Angiosarcoma of the breast after wide local excision and radiotherapy for breast carcinoma.* Clin Radiol, 2002. **57**(1): p. 63-6.
68. Barrow, B.J., et al., *Role of radiotherapy in sarcoma of the breast--a retrospective review of the M.D. Anderson experience.* Radiother Oncol, 1999. **52**(2): p. 173-8.
69. Marchant, L.K., et al., *Bilateral angiosarcoma of the breast on MR imaging.* AJR Am J Roentgenol, 1997. **169**(4): p. 1009-10.
70. Badwe, R.A., et al., *Angiosarcoma of the skin overlying an irradiated breast.* Breast Cancer Res Treat, 1991. **19**(1): p. 69-72.
71. Moskaluk, C.A., et al., *Low-grade angiosarcoma of the skin of the breast: a complication of lumpectomy and radiation therapy for breast carcinoma.* Hum Pathol, 1992. **23**(6): p. 710-4.
72. Otis, C.N., et al., *The rapid onset of cutaneous angiosarcoma after radiotherapy for breast carcinoma.* Cancer, 1986. **57**(11): p. 2130-4.
73. Komdeur, R., et al., *Clinicopathologic assessment of postradiation sarcomas: KIT as a potential treatment target.* Clin Cancer Res, 2003. **9**(8): p. 2926-32.
74. Quadros, C.A., et al., *Good outcome after neoadjuvant chemotherapy and extended surgical resection for a large radiation-induced high-grade breast sarcoma.* Int Semin Surg Oncol, 2006. **3**: p. 18.
75. Lagrange, J.L., et al., *Sarcoma after radiation therapy: retrospective multiinstitutional study of 80 histologically confirmed cases. Radiation Therapist and Pathologist Groups of the Federation Nationale des Centres de Lutte Contre le Cancer.* Radiology, 2000. **216**(1): p. 197-205.
76. Billings, S.D., et al., *Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases.* Am J Surg Pathol, 2004. **28**(6): p. 781-8.
77. Marchal, C., et al., *Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French comprehensive Cancer Centers.* Int J Radiat Oncol Biol Phys, 1999. **44**(1): p. 113-9.
78. Brady, M.S., J.J. Gaynor, and M.F. Brennan, *Radiation-associated sarcoma of bone and soft tissue.* Arch Surg, 1992. **127**(12): p. 1379-85.
79. Kuten, A., et al., *Postirradiation soft tissue sarcoma occurring in breast cancer patients: report of seven cases and results of combination chemotherapy.* J Surg Oncol, 1985. **28**(3): p. 168-71.
80. Khan, M., et al., *Radiation-induced spindle cell sarcoma: a rare case report.* Indian J Dent Res, 2009. **20**(3): p. 380-4.

81. Bjerkehagen, B., et al., *Radiation-induced sarcoma: 25-year experience from the Norwegian Radium Hospital.* Acta Oncol, 2008. **47**(8): p. 1475-82.
82. Cha, C., et al., *Long-term results with resection of radiation-induced soft tissue sarcomas.* Ann Surg, 2004. **239**(6): p. 903-9; discussion 909-10.
83. Plotti, F., et al., *An unusual case of secondary fibrosarcoma after treatment for breast cancer.* Gynecol Oncol, 2006. **103**(3): p. 1133-6.
84. Borman, H., T. Safak, and D. Ertoy, *Fibrosarcoma following radiotherapy for breast carcinoma: a case report and review of the literature.* Ann Plast Surg, 1998. **41**(2): p. 201-4.
85. Souba, W.W., et al., *Radiation-induced sarcomas of the chest wall.* Cancer, 1986. **57**(3): p. 610-5.
86. Chapelier, A.R., et al., *Radical resection of radiation-induced sarcoma of the chest wall: report of 15 cases.* Ann Thorac Surg, 1997. **63**(1): p. 214-9.
87. Adhikari, D., S.I. Hajdu, and D. Levine, *Post-radiation angiosarcoma and bilateral mastectomy.* Ann Clin Lab Sci, 2002. **32**(4): p. 428-33.
88. Wijnmaalen, A., et al., *Angiosarcoma of the breast following lumpectomy, axillary lymph node dissection, and radiotherapy for primary breast cancer: three case reports and a review of the literature.* Int J Radiat Oncol Biol Phys, 1993. **26**(1): p. 135-9.
89. Colville, R.J., et al., *Angiosarcoma of the breast after quadrantectomy and postoperative radiotherapy for carcinoma.* Br J Plast Surg, 2000. **53**(7): p. 622-4.
90. Turner, W.H. and M.J. Greenall, *Sarcoma induced by radiotherapy after breast conservation surgery.* Br J Surg, 1991. **78**(11): p. 1317-8.
91. Brenin, C.M., et al., *Radiation-Induced Sarcoma Following Treatment of Breast Cancer.* Cancer Control, 1998. **5**(5): p. 425-432.
92. Cafiero, F., et al., *Radiation-associated angiosarcoma: diagnostic and therapeutic implications--two case reports and a review of the literature.* Cancer, 1996. **77**(12): p. 2496-502.
93. Rosen, P.P., M. Kimmel, and D. Ernsberger, *Mammary angiosarcoma. The prognostic significance of tumor differentiation.* Cancer, 1988. **62**(10): p. 2145-51.
94. Feigenberg, S.J., et al., *Angiosarcoma after breast-conserving therapy: experience with hyperfractionated radiotherapy.* Int J Radiat Oncol Biol Phys, 2002. **52**(3): p. 620-6.
95. Weber, B. and C. Marchal, *Three cases of breast angiosarcomas after breast-conserving treatment for carcinoma.* Radiother Oncol, 1995. **37**(3): p. 250-2.
96. Yap, B.S., et al., *Chemotherapy for postmastectomy lymphangiosarcoma.* Cancer, 1981. **47**(5): p. 853-6.
97. Mano, M.S., et al., *Radiation-induced angiosarcoma of the breast shows major response to docetaxel after failure of anthracycline-based chemotherapy.* Breast, 2006. **15**(1): p. 117-8.
98. Perez-Ruiz, E., et al., *Response to paclitaxel in a radiotherapy-induced breast angiosarcoma.* Acta Oncol, 2009. **48**(7): p. 1078-9.
99. Gambini, D., et al., *Paclitaxel-dependent prolonged and persistent complete remission four years from first recurrence of secondary breast angiosarcoma.* Tumori, 2009. **95**(6): p. 828-31.
100. DeLaney, T.F., *Optimizing radiation therapy and post-treatment function in the management of extremity soft tissue sarcoma.* Curr Treat Options Oncol, 2004. **5**(6): p. 463-76.

101. Mouridsen, H.T., et al., *Adriamycin versus epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III study of the EORTC Soft Tissue and Bone Sarcoma Group.* Eur J Cancer Clin Oncol, 1987. **23**(10): p. 1477-83.
102. Santoro, A., et al., *Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.* J Clin Oncol, 1995. **13**(7): p. 1537-45.
103. Verweij, J., et al., *Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the european organization for research and treatment of cancer soft tissue and bone sarcoma group.* J Clin Oncol, 2000. **18**(10): p. 2081-6.
104. Schlemmer, M., et al., *Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group.* Eur J Cancer, 2008. **44**(16): p. 2433-6.
105. Penel, N., et al., *[Frequency of genetic diseases and cancer antecedents in 493 adults with visceral or soft tissue sarcomas]*. Bull Cancer, 2003. **90**(10): p. 887-95.
106. Skubitz, K.M. and P.A. Haddad, *Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma.* Cancer, 2005. **104**(2): p. 361-6.
107. Okuno, S.H. and J.H. Edmonson, *Progress in the Systemic Treatment of Advanced Soft-Tissue Sarcomas.* Cancer Control, 1998. **5**(1): p. 34-39.
108. Neuhaus, S.J., et al., *Treatment and outcome of radiation-induced soft-tissue sarcomas at a specialist institution.* Eur J Surg Oncol, 2009. **35**(6): p. 654-9.
109. Buatti, J.M., et al., *Radiation-induced angiosarcoma of the breast. Case report and review of the literature.* Am J Clin Oncol, 1994. **17**(5): p. 444-7.
110. Taat, C.W., et al., *Dermal angiosarcoma of the breast: a complication of primary radiotherapy?* Eur J Surg Oncol, 1992. **18**(4): p. 391-5.
111. Palta, M., et al., *Angiosarcoma after breast-conserving therapy: long-term outcomes with hyperfractionated radiotherapy.* Cancer. **116**(8): p. 1872-8.
112. Schulz, U., J.M. Gokel, and W. Poleska, *Soft tissue sarcomas after radiation treatment for breast cancer. Three case studies and review of literature.* Strahlenther Onkol, 2000. **176**(3): p. 144-9.
113. Givens, S.S., et al., *Non-metastatic Ewing's sarcoma: twenty years of experience suggests that surgery is a prime factor for successful multimodality therapy.* Int J Oncol, 1999. **14**(6): p. 1039-43.
114. Kirova, Y.M., et al., *Radiation-induced sarcomas after radiotherapy for breast carcinoma: a large-scale single-institution review.* Cancer, 2005. **104**(4): p. 856-63.
115. de Giorgi, V., et al., *Synchronous angiosarcoma, melanoma and morphea of the breast skin 14 years after radiotherapy for mammary carcinoma.* Acta Derm Venereol. **90**(3): p. 283-6.