Surgical Oncology 41 (2022) 101726

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Radiation-associated angiosarcoma of the breast: An international multicenter analysis

Jana Mergancová [a,b], Anna Lierová [c], Oldřich Coufal [d,e], Jan Žatecký [d,f], Bohuslav Melichar [b,g], Ilona Zedníková [h], Jindřiška Mergancová [a], Anna Jesenková [a,z], Karel Šťastný [a], Jiří Gatěk [i], Otakar Kubala [j], Jiří Prokop [j], Daniel Dyttert [k], Marián Karaba [l], Ivana Schwarzbacherová [m], Anna Humeňanská [n], Jindřich Šuk [m], Michal Valenta [o], Vladimír Moucha [p], Lukáš Sákra [a], Aleš Hlávka [q], Mária Hácová [r], Radovan Vojtíšek [t], Marek Sochor [u], Tomáš Jirásek [v], Michaela Zábojníková [w], Martina Zemanová [x], Katarína Macháleková [y], Dominika Rusnáková [l], Eva Kúdelová [s], Marek Smolár [s,*]

[a] Department of Surgery, Pardubice General Hospital, Pardubice, Czech Republic
[b] Faculty of Medicine and Dentistry, Palacký University Olomouc, Olomouc, Czech Republic
[c] Faculty of Health Studies, Department of Clinical Subspecialities, University of Pardubice, Pardubice, Czech Republic
[d] Department of Surgical Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic
[e] Department of Surgical Oncology, Masaryk University, Faculty of Medicine, Brno, Czech Republic
[f] Department of Surgery, Silesian Hospital in Opava, Opava, Czech Republic
[g] Department of Oncology, University Hospital Olomouc, Olomouc, Czech Republic
[h] Department of Surgery, University Hospital Pilsen, Pilsen, Czech Republic
[i] Department of Surgery, EUC Clinic Zlín, Zlín, Czech Republic
[j] Department of Surgery, University Hospital Ostrava, Ostrava, Czech Republic
[k] Department of Surgical Oncology, St. Elizabeth Cancer Institute, Bratislava, Slovak Republic
[l] Department of Oncosurgery, National Cancer Institute, Slovak Medical University, Bratislava, Slovak Republic
[m] 1th Surgical Department, General University Hospital in Prague, Prague, Czech Republic
[n] Department of Surgery, Hospital AGEL Ostrava-Vítkovice, Ostrava, Czech Republic
[o] Department of Surgery, Liberec General Hospital, Liberec, Czech Republic
[p] Mammological Ambulance, Hořovice, Czech Republic
[q] Department of Oncology, Pardubice General Hospital, Pardubice, Czech Republic
[r] Department of Pathology, Pardubice General Hospital, Pardubice, Czech Republic
[s] Clinic of General, Visceral and Transplant Surgery, Jessenius Faculty of Medicine, Comenius University in Bratislava, University Hospital Martin, Martin, Slovak Republic
[t] Department of Oncology and Radiotherapy, University Hospital Pilsen, Pilsen, Czech Republic
[u] Department of Radiation and Clinical Oncology, Liberec General Hospital, Liberec, Czech Republic
[v] Department of Pathology, Liberec General Hospital, Liberec, Czech Republic
[w] Department of Oncology, EUC Clinic Zlín, Zlín, Czech Republic
[x] Department of Radiooncology, St. Elizabeth Cancer Institute, Bratislava, Slovak Republic
[y] Department of Pathology, St. Elizabeth Cancer Institute, Bratislava, Slovak Republic
[z] Charles University, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech Republic

ARTICLE INFO

Keywords:
Radiation
Angiosarcoma
Breast
Multicenter study

ABSTRACT

Introduction: Radiation-associated angiosarcoma (RAAS) is a rare and serious complication of breast irradiation. Due to the rarity of the condition, clinical experience is limited and publications on this topic include only retrospective studies or case reports.

Abbreviations: RAAS, radiation-associated angiosarcoma; RT, radiotherapy; AS, angiosarcoma; LRFS, local recurrence-free survival; BC, breast cancer; ALND, axillary lymph node dissection; DCIS, ductal carcinoma in situ.

* Corresponding author. Clinic of General, Visceral and Transplant Surgery, Jessenius Faculty of Medicine, Comenius University in Bratislava, University Hospital Martin, Kollárova 2, Martin, 036 59, Slovakia.
E-mail address: marino.smolar@gmail.com (M. Smolár).

https://doi.org/10.1016/j.suronc.2022.101726
Received 21 November 2021; Received in revised form 27 January 2022; Accepted 13 February 2022
Available online 16 February 2022

Materials and methods: All patients diagnosed with RAAS between January 2000 and December 2017 in twelve centers across the Czech Republic and Slovakia were evaluated.
Results: Data of 53 patients were analyzed. The median age at diagnosis was 72 (range 44–89) years. The median latency period between irradiation and diagnosis of RAAS was 78 (range 36–172) months. The median radiation dose was 57.6 (range 34–66) Gy. The whole breast radiation therapy with radiation boost to the tumor bed was the most common radiotherapy regimen. Total mastectomy due to RAAS was performed in 43 patients (81%), radical excision in 8 (15%); 2 patients were not surgically treated due to unresectable disease. Adjuvant chemotherapy followed surgical therapy of RAAS in 18 patients, 3 patients underwent adjuvant radiotherapy. The local recurrence rate of RAAS was 43% and the median time from surgery to the onset of recurrence was 7.5 months (range 3–66 months). The 3-year survival rate was 56%, the 5-year survival rate was only 33%. 46% of patients died during the follow-up period.
Conclusion: The present data demonstrate that RAAS is a rare condition with high local recurrence rate (43%) and mortality (the 5-year survival rate was 33%.). Early diagnosis of RAAS based on biopsy is crucial for treatment with radical intent. Surgery with negative margins constitutes the most important part of the therapy; the role of adjuvant chemotherapy and radiotherapy is still unclear.

1. Introduction

Breast-conserving surgery followed by adjuvant radiotherapy (RT) is the current standard of care in the treatment of early breast cancer. The complications of RT are of either stochastic or deterministic nature. As the principal stochastic effect, ionizing radiation causes a small yet detectable risk of secondary malignancies, both epithelial (carcinomas) and mesenchymal (sarcomas). Although angiosarcomas are among the less common types of post-radiation sarcomas, they represent the most common type of sarcomas observed after irradiation of the breast parenchyma [1]. The cumulative incidence of radiation-associated angiosarcoma (RAAS) is 3.2 per 1000 patients after 15 years [2]. The results of a recent Dutch population study reported the risk of developing RAAS of the breast to be 0.1% [3].

The first diagnostic criteria for RAAS, established for post-radiation bone sarcoma by Cahan et al. as early as 1948, included four fundamental points: (1) there must be evidence of an initial malignant tumor histologically different from the radiation-induced sarcoma; (2) the sarcoma must develop in the irradiated field; (3) the latency period between the two malignancies must be long (typically 4 years or more); and (4) the second malignancy must be histopathologically confirmed as a sarcoma [4]. These criteria soon became the generally accepted basis for RAAS diagnosis. Subsequently, these criteria were modified by Arlen et al., in 1971 [5]. The minimum latency period was shortened to 3 years, and the need for histological differentiation between the primary and secondary angiosarcoma (AS) was added [5].

Secondary angiosarcomas result from a previous RT, typically occur in radiotherapy-altered skin of older women, and may subsequently infiltrate the adjacent mammary parenchyma. The overall five-year survival rates in institutional series of secondary AS are between 43 and 88% [6,7].

To date, there is no established evidence-based standard treatment of RAAS. Surgery is at present the predominant treatment method. The role of chemotherapy in addressing RAAS is still under study, and regimens vary in the literature [8]. Radiotherapy in RAAS, as adjuvant or neo--adjuvant treatment, is unclear and controversial. Novel methods with adding hyperthermia to radiotherapy are showing promising results [9].

2. Material and methods

2.1. Patients

This international Czech and Slovak multicenter retrospective study included 9 Czech (Hospital Pardubice Region, Masaryk Memorial Cancer Institute in Brno, General University Hospital in Prague, Hořovice Hospital, Liberec Regional Hospital, Faculty Hospital in Ostrava, Vítkovice Hospital in Ostrava, Tomas Bata Regional Hospital in Zlín and University Hospital in Pilsen) and 3 Slovak (University Hospital in Martin, National Oncological Institute in Bratislava and St. Elizabeth Cancer Institute in Bratislava) hospitals. Patient information was collected and evaluated. Inclusion criteria were: (i) previously diagnosed breast cancer (BC); (ii) BC treatment with surgery and subsequent RT; (iii) histologically proven angiosarcoma of the breast after irradiation diagnosed between 1st of January 2000 and 31st of December 2017; and (iv) absence of metastases at the time of RAAS diagnosis. The study participants have agreed with anonymous usage of their data for retrospective analysis. The patient's previous refusal to participate in any study was an exclusion criterion. This study was conducted in accordance with the Declaration of Helsinki. The primary outcomes included the local recurrence-free survival, 3- and 5- year survival, and the effect of chemotherapy on local recurrence and survival rate in patients with RAAS.

2.2. Collected variables and outcome measures

Medical records and pathology reports were used to assess patients' eligibility. Detailed information about individual patients' age and sex, primary tumor (type, size, and grade), surgery (type, biopsy of sentinel lymph node or status of axillary nodes), radiotherapy (dose, region, boost), and/or other treatments (hormonal or chemotherapy) were collected and analyzed. The period of latency and method of angiosarcoma treatment (surgery, radiotherapy, and/or chemotherapy) were documented as well. Patients were followed up and outcomes analyzed, including the local recurrence-free survival (LRFS) and 3- and 5- year survival.

2.3. Statistical analysis

Continuous variables were characterized by median and range. Categorical data were summarized as absolute and relative frequencies. The latency period was defined as the time from the date of the completion of radiotherapy and the date of RAAS diagnosis. LRFS of RAAS was calculated as the time from histological diagnosis to the development of the (first) local recurrence. Survival curves were calculated using the Kaplan–Meier method. The effect of chemotherapy treatment (with/without chemotherapy) on 3- and 5- year survival was compared by $\chi 2$ test; p-value of 0.05 and lower was considered statistically significant. All obtained data were analyzed in STATISTICA software, version 12 (StatSoft, Dell, 2016, TX, USA).

3. Results

Records of 70 patients were analyzed. 17 patients were subsequently excluded, including 1 patient with a definitive diagnosis of hemangioendothelioma, 3 patients with primary AS, 2 patients with benign pathology after a previous positive core-cut biopsy for RAAS, 4 patients with RAAS diagnosed in 2018 after the end of the study period, 2 patients with the latency period between breast cancer and RAAS shorter

than 36 months, and 5 patients due to the lack of data.

The final cohort included 53 patients, all Caucasian females, all of whom met the Cahan criteria.

3.1. Primary breast malignancy features and treatment

Primary breast cancer characteristics of all patients are shown in Table 1. The median age at diagnosis was 66 (range 31–83) years. The majority of patients (72%) were diagnosed with invasive carcinoma of no special type (NST), 10 patients (19%) with other types of invasive breast cancer; invasive lobular carcinoma was diagnosed in 4 patients (8%) and DCIS (ductal carcinoma in situ) in 1 patient (2%). All patients underwent breast-conserving surgery. During the surgery, most patients (n = 48) underwent axillary lymph node dissection (ALND); sentinel node biopsy was performed in 10 patients, of which 5 were positive and subsequently underwent axillary node dissection.

The median radiotherapy dose was 57.6 (range 34–66) Gy. The total radiation dose and fractionation varied among centers and countries. The most common radiotherapy (RT) regimen was whole breast RT with tumor bed boost in 24 patients (45%), other RT regimens included irradiation of the breast, axilla, and other regions (Table 1). Twelve patients (23%) were treated by irradiation of the breast without the boost or lymph node irradiation. The most common fractionation schedule was 2 Gy per fraction (60%); in remaining patients, the dose per fraction ranged between 1.8 and 3.4 Gy. In addition to RT, 18 patients (34%) were treated with adjuvant or neoadjuvant chemotherapy (28% and 6%, respectively). The majority of patients (92%) also received hormonal therapy and in one patient (2%), targeted trastuzumab treatment was applied.

Table 1
Summary of breast cancer characteristic and patient treatment.

	Total no. of patient (%) N = 53
Age at BC diagnosis	Median 66.0 years (range 31.0–83.0 years)
Primary BC tumor size (mm)	
≤ 20	30 (57)
> 20	14 (26)
n.a.	9 (17)
Surgery	
BCS	53 (100)
Histological Classifications of BC	
IDC	38 (72)
ILC	4 (8)
DCIS	1 (2)
other invasive BC	10 (19)
Grade	
1	14 (26)
2	23 (43)
3	9 (17)
n.a.	7 (13)
Sentinel nodes biopsy	
Yes	10 (19)
Positive	5 (9)
No	43 (81)
Axillary dissection	
Yes	48 (91)
Positive lymph nodes	13 (25)
No	5 (9)
Radiation dose	Median 57.6 Gy (range 34.0–66.0 Gy)
Radiation region and boost	
breast	12 (23)
breast and axilla	1 (2)
breast, axilla and other	4 (8)
breast plus boost to TB	24 (45)
breast and axilla plus boost to TB	3 (6)
breast, axilla and other plus boost to TB	8 (15)
other region	1 (2)
Chemotherapy	
Yes	18 (34)
Adjuvant	15 (28)
Neoadjuvant	3 (6)
No	35 (66)
Hormonal therapy	
Yes	49 (92)
No	4 (8)

BC - breast cancer, BCS – breast conserving surgery, ILC - invasive lobular carcinoma, DCIS - ductal carcinoma in situ, IDC - invasive ductal carcinoma, RT - radiotherapy, TB - tumor bed, n.a. - not available.

3.2. Characterization of secondary angiosarcoma of the breast

Characteristics of radiation-induced angiosarcoma of the breast, treatment modalities, and patient outcomes are summarized in Table 2. The median age at presentation was 72 (range 44–89) years. The median latency period between the RT of the primary malignancy and the diagnosis of angiosarcoma was 78 (range 36–172) months. Only palliative care was used in two patients (4%) who did not undergo surgery due to unresectable disease (Fig. 1). One patient was treated with palliative chemotherapy and died 6 months after being diagnosed with RAAS. The other patient was treated with palliative radiotherapy and died 13 months after diagnosis. Most of the remaining 51 patients were treated curatively and underwent either total mastectomy (81%) or radical excision (15%). All surgical resections of RAAS were radical (R0). Adjuvant radiotherapy for angiosarcoma was administered in 2 patients (4%) and in 18 patients (34%), chemotherapy was used as adjuvant treatment. No significant difference between these patients and patients not treated with chemotherapy was detected in survival rate ($p = 0.074$) or local recurrence ($p = 0.449$). One patient received neoadjuvant chemotherapy (paclitaxel weekly) with a partial clinical response. The patient died of the third recurrence of the RAAS, 59 months after being diagnosed with RAAS. At the time of diagnosis of RAAS, all patients presented without distant metastases (M0).

In two patients, an atypical vascular proliferation of uncertain

Table 2
Summary of patient characteristic with radiation-associated angiosarcoma and treatment.

	Total no. of patient (%) N = 53
Age at RAAS diagnosis	Median 72.0 years (range 44–89 years)
Latency time from primary BC	Median 78.0 months (range 36–172 months)
Surgery	
mastectomy	43 (81)
radical excision	8 (15)
inoperable	2 (4)
Radiotherapy of RAAS	
yes	3 (6)
no	49 (92)
n.a.	1 (2)
Chemotherapy of RAAS	
Yes	18 (34)
No	34 (64)
n.a.	1 (2)
Treatment modality	
Radical	51 (96)
Palliative	2 (4)
RAAS outcome data	
without local evidence of disease	21 (40)
recurrence	23 (43)
progression	9 (17)
Number of recurrence	
only 1	15 (28)
2 - 4	7 (13)
5 and more	1 (2)
Patients status at the last follow - up	
alive	26 (49)
dead	22 (42)
n.a.	5 (9)

RAAS – radiation-associated angiosarcoma, BC - breast cancer, n.a. - not available.

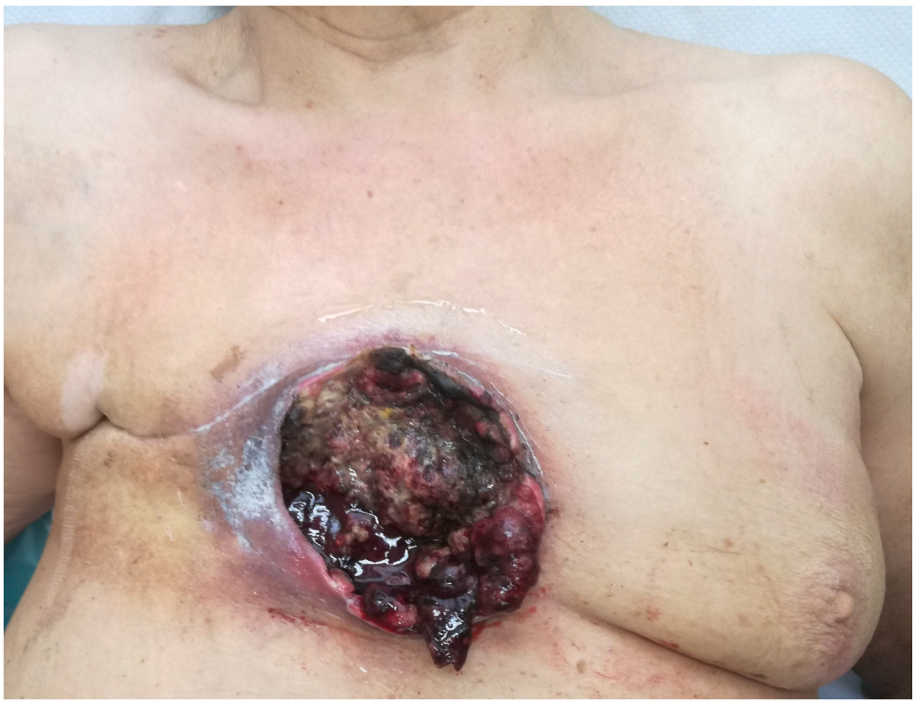

Fig. 1. Unresectable advanced radiation-induced angiosarcoma.

biological nature was found after the first diagnostic excision. Because of the persistence of suspected lesions, the diagnostic excision was repeated in both cases and, subsequently, the diagnosis of RAAS was established. On the contrary, a false-positive result was described based on the core cut biopsy in two cases where after the complete surgical removal of the lesion, the histological examination (as well as a second opinion re-examination) disproved malignancy. One of the patients in the present cohort underwent a core-cut biopsy, which was originally misdiagnosed as an invasive triple-negative ductal carcinoma of the breast, and the patient was treated with chemotherapy for the recurrence of breast cancer. Only after mastectomy, the definitive histological analysis reclassified the tumor as RAAS.

3.3. RAAS follow-up outcomes

Of the whole cohort, no evidence of recurrence was present in 21 (40%) patients. Recurrence (manifestation of the disease more than 3 months after the surgery) was so far observed in 23 (43%) patients (Fig. 2). Distant metastases were revealed in 9 (17%) patients during follow-up, two of whom were inoperable. 9 patients were excluded from the calculation of the local recurrence rate due to the progression of the disease (manifestation of the disease 3 months or sooner after the surgery); the local recurrence rate was, therefore, calculated from a subgroup of 44 patients. LRFS was 42% after 5 years (Fig. 3). The median time to recurrence was 7.5 months (range 3–66 months). Among patients with recurrences, a single episode of recurrence was recorded in 15 patients (28%), 2 to 4 episodes in 7 patients (13%), and 5 or more episodes of recurrence were recorded in 1 patient (2%). In absolute numbers, the highest number of disease recurrences was observed in the group with RT of the whole breast with a tumor bed boost (n = 24). At the first recurrence, mastectomy was performed in patients in whom it was not performed before; subsequent recurrences were resolved by margin-negative radical resection (R0 resection).

The patients were treated between 2000 and the end of 2018. By the

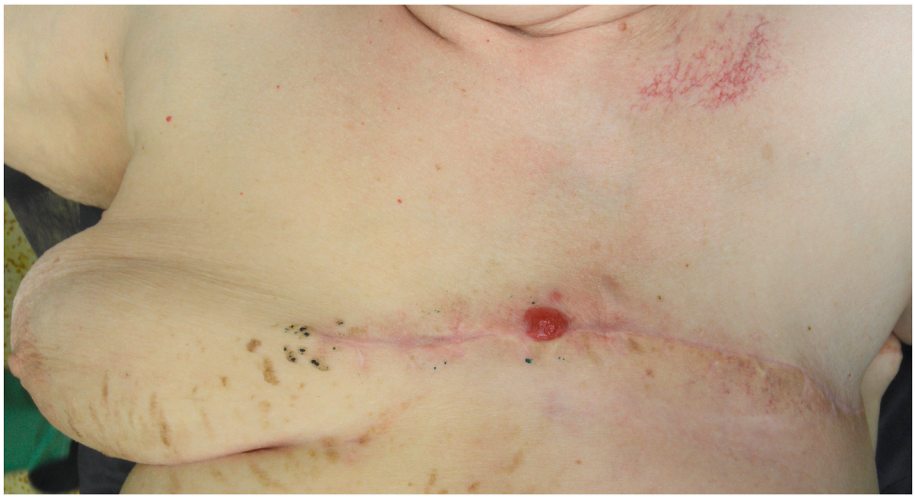

Fig. 2. Recurrence of RAAS (red lesion in the area of the scar after mastectomy).

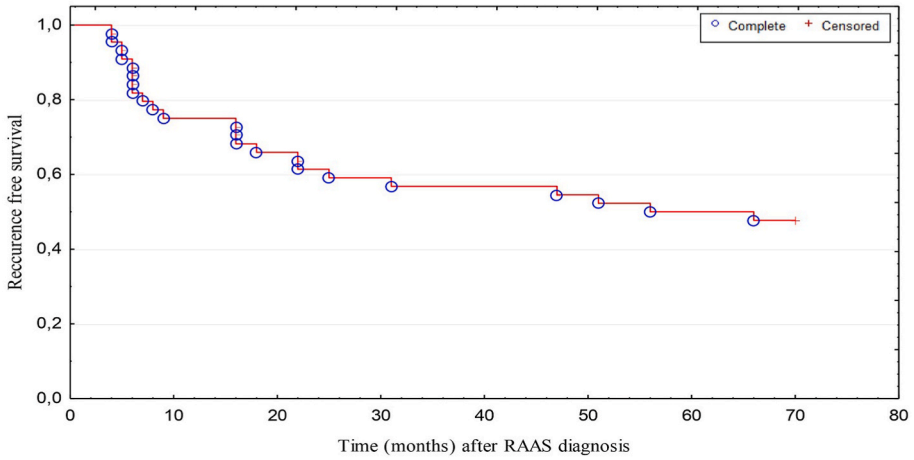

Fig. 3. Graphic representation of Local recurrence-free analysis - LRFS (n = 44).

time of the analysis, 5 patients were lost for follow-up and excluded at the last visit. Of the remaining 48 patients, 26 (54%) were alive at the time of the analysis and 22 (46%) were known dead. The majority (n = 16) of patients alive at the last follow-up were without any evidence of the disease while 9 patients developed recurrence. The median follow-up from the diagnosis of angiosarcoma in the present study was 30 months (range of 5–186 months). The patients whose follow–up was shorter than 36 and 60 months, respectively, were excluded from the analysis of the 3- and 5- year survivals. The 3-year survival rate (Fig. 4; 43 patients) was 56% compared to the 5-year survival rate (Fig. 5; 33 patients), which was only 33%. Angiosarcoma was the most common cause of death (n = 19).

4. Discussion

The first mention of a primary AS of the breast appeared in the literature at the beginning of the last century (1907) in a paper by Borrman [10]. The development of secondary AS in chronic lymphedema after radical mastectomy for breast cancer was described in 1948 by Stewart and Treves, after whom the condition was named (Stewart-Treves Syndrome) [11]. RAAS was first described in 1981 by Maddox and Evans [12]. It is a rare radiotherapy-induced malignancy and standardized treatment has not yet been defined. It is evident from the literature that each center follows local guidelines and treatment largely depends on the current condition of the patient.

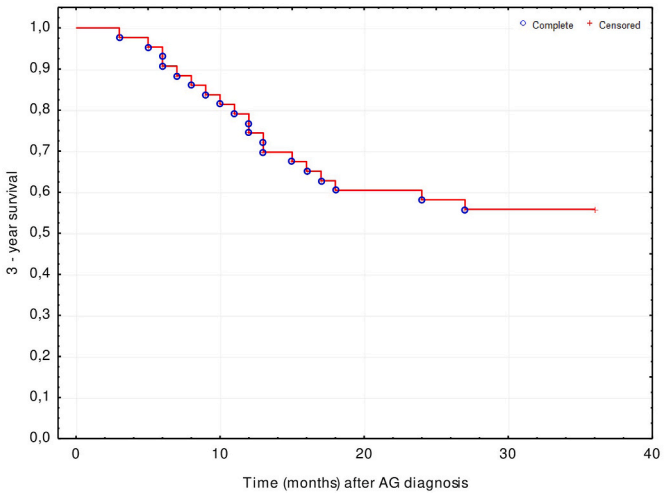

Fig. 4. Graphic representation of 3 – year survival analysis (n = 43).

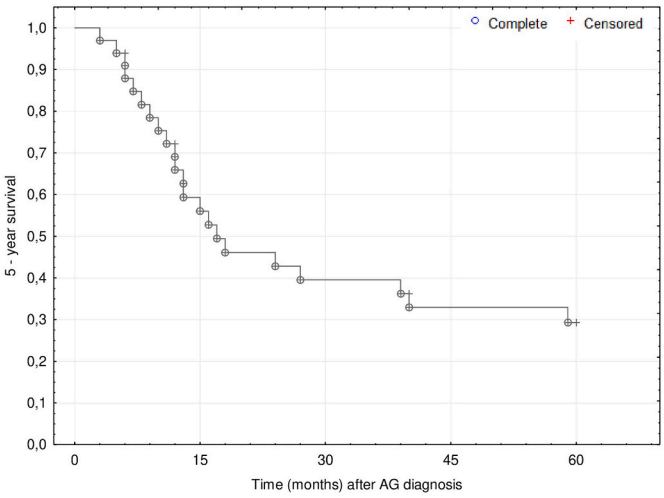

Fig. 5. Graphic representation of 5 – year survival analysis (n = 33).

Various studies report the median age at RAAS diagnosis to range between 58 and 71.5 years [3,13,14], similarly to the present cohort (median of 72 years). The literature reports a median latency period from the end of the radiotherapy to the RAAS diagnosis between 6 and 8 years [3,4,14], similarly to the 6.5 years (78 months) with the range of 3–14 years (36–172 months) in the cohort presented in this study.

Several studies on RAAS have been published. All available studies in the Medline database were retrospective, containing individual cases or case series. In addition, the outcomes and conclusions were often inconsistent. To the best of our knowledge, the present retrospective study is one of the biggest cohorts of RAAS patients published so far.

RAAS prognostic factors are still unclear and do not provide reliable statistically significant information. Cohen-Hallaleh et al. [15] performed a multivariate analysis of a RAAS patient cohort and reported the tumor size to be the only independent prognostic factor for DMFS (distant metastases-free survival) and OS in a group of patients with resectable RAAS. Barrow et al. [16] reported the median OS in patients with RAAS of up to 2 cm to be 80 months while in those with tumors larger than 5 cm, the median OS was only 20 months. The number of skin lesions was proposed as another prognostic factor. The 2-year survival rate of patients with a single skin lesion was 50% [17], that of patients with multiple skin lesions was 0% [18]. Other authors have identified three major adverse prognostic factors, namely higher age, tumor size, and RAAS histological grade [19].

Several studies noted the absence of the regional lymph node

involvement in RAAS as sarcomas very rarely metastasize to the lymphatic system [20,21]. However, virtually all RAAS patients underwent axillary surgery in the past, either sentinel lymph node biopsy (SLNB) or complete ALND as a part of the primary surgical treatment for breast cancer. A total of 48 (91%) patients in the present cohort underwent prior ALND, 14 (30%) of them with subsequent adjuvant RT to the regional lymph nodes. Impaired lymphatic drainage induced by this therapy could accelerate the etiopathogenetic process of RAAS development, similar to Stewart-Treves syndrome [22]. The SLNB started to be used in 2002 in the Czech Republic and one year later in Slovakia. This is another reason for such a low rate of SLNBs in the cohort presented in this paper as most of the patients underwent treatment for breast cancer before 2002.

Multiple papers agree on the importance of early diagnosis of RAAS which opens the potential for curative therapy [6,13,15]. However, the rarity of the disease, non-specific clinical and radiological presentation, as well as unusual histology, often lead to delayed diagnosis. Imaging may not always detect RAAS, so the greatest emphasis is placed on the clinical examination, description of the macroscopic appearance of skin lesions and of all new skin changes (Fig. 6), as well as the consistent education about breast self-examination [23]. RAAS often develops many years after the primary therapy when the frequency of follow-up visits is low. The mammographic finding is usually non-specific or even missing [24]. On ultrasonographic examination, RAAS appears as a heterogeneous, hypervascularized mass with hyper- and hypoechogenic areas disrupting the architecture of the gland [25]. Of the imaging methods, MRI performs best in detecting the recurrence or a residual tumor after surgical excision [26]. According to some authors, the most suitable method for diagnosing RAAS are the core cut biopsy or a diagnostic excision, which should be performed whenever a new suspicious lesion appears in a previously irradiated area [27–29]. According to our own experience, even a core cut biopsy (much less needle biopsy) may fail to provide a sufficient sample for a valid pathological evaluation and may yield a false negative result. In our cohort, this was the case in one patient in whom the necessity of subsequent surgical excision with further histological processing resulted in a delay of diagnosis and treatment. Even a probatory surgical excision may fail to allow an adequate histological evaluation.

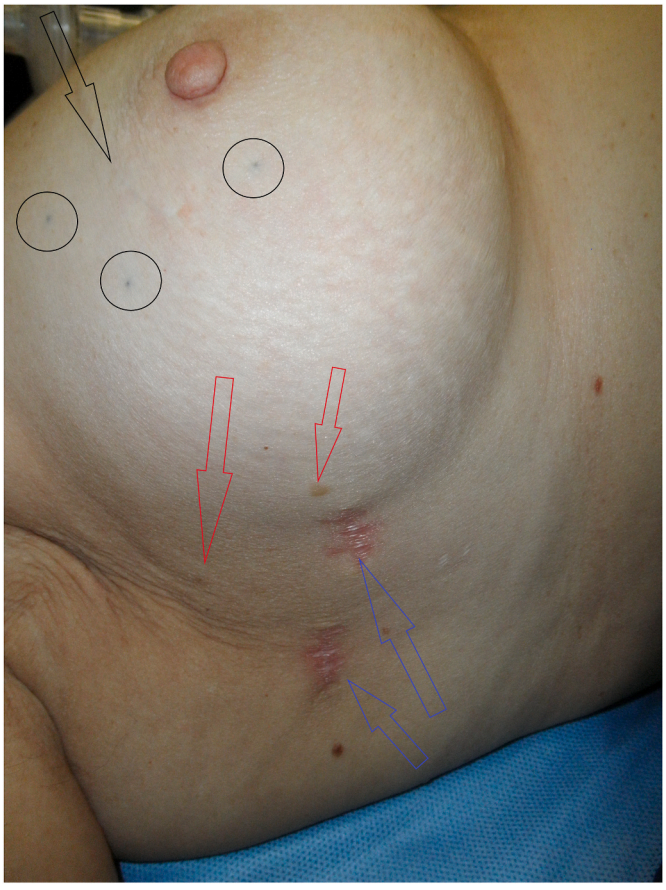

Fig. 6. Discrete clinical manifestation of RAAS (red arrows). Blue arrows show scars after an excisional biopsy of similar lesions. Patient after neoadjuvant therapy (black circles indicate carbon marks of the original tumor) and subsequent partial mastectomy (scar shown by a black arrow).

Neither is there any consensus also missing on the initial treatment of RAAS. Radical surgery is the cornerstone of therapy [4,17,19,30]. However, uncertainties persist concerning the recommendation on the resection margins as well as the type of surgical procedure, i.e. either broad excision or total mastectomy. The resection margins during surgical treatment have been investigated in several studies. For lesions with skin infiltration, some authors recommend a wide excision or mastectomy with resection margins of 2–4 cm while in smaller lesions, a margin of 1 cm is considered safe [31–34]. The survival rate is significantly lower in the case of positive resection margins (R1 and R2, respectively) compared to the clear margin (R0 resection) [35,36]. One study demonstrated a significantly improved disease-specific survival and lower local recurrence rates if radical resection (excision of all previously irradiated skin with concomitant mastectomy) was employed compared with more conservative skin resection (simple mastectomy with limited skin excision) [37].

Opinions on non-surgical therapy differ significantly. According to some authors, neoadjuvant or adjuvant chemotherapy improves local control [4] but not the systemic relapse or overall survival, which is reported to range between 5 and 48 months [29,38]. In our cohort, 18 patients had adjuvant chemotherapy after radical excision; of these, 6 patients were subsequently without recurrence, 4 patients were surviving with a local recurrence and 8 died of RAAS (8–126 months after the diagnosis of RAAS). No statistically significant difference in survival rate or local recurrence rate was observed compared to patients not treated with chemotherapy; however, it is necessary to point out that the size of the cohort was limited and chemotherapy regimens very heterogeneous. Some authors have reported promising responses to paclitaxel or gemcitabine-taxane (including complete remissions) in resectable primary or recurrent RAAS [39,40].

The Cohen-Hallaleh study evaluated the effect of neoadjuvant chemotherapy in primarily inoperable tumors [13]. Phase II studies suggest a clinical benefit of paclitaxel treatment in a primarily unresectable RAAS with a 74% rate of non-progression after two cycles of therapy [41–43]. A patient from our cohort who received neoadjuvant chemotherapy (Paclitaxel weekly) died 59 months after the diagnosis of RAAS during the third recurrence of the RAAS.

The fact that RAAS are radiation-induced tumors makes further use of radiotherapy in the treatment of secondary AS controversial, especially with regard to the total doses administered. RAAS is a stochastic effect of radiation independent of the prior dose; however, deterministic effects will also depend on the dose of previous irradiation. Depla et al. (2014) reported that the addition of radiotherapy after surgical treatment resulted in improved local control [44]. Similarly, Donovan et al. (2018) concluded that hyperfractionated RT is associated with a lower incidence of local recurrences after RAAS surgical excision [45]. A combination of accelerated hyperfractionated radiation with hyperthermia with near-complete pathological response was published by Molitoris et al. [46]. Hyperthermia is considered to be a potential radiosensitizer and could be an option in combination with radiotherapy in the adjuvant setting [46,47].

In our cohort, two patients underwent adjuvant RT after primary radical mastectomy with a total dose of 39 and 40 Gy, respectively. Both patients died (5 and 17 months after diagnosis of RAAS, respectively).

The highest disease recurrence rate was observed in the group treated by RT of the whole breast with tumor bed boost, which is

probably related to the fact that it was the area most frequently subjected to adjuvant RT.

A novel technique of contact-free, thermography-controlled water-filtered infrared-A superficial hyperthermia (wIRA-HT) was developed to cover large treatment fields up to a depth of approximately 2 cm. This procedure reduces RT-related toxicity to a minimum and even allows for repeat re-irradiation using the same dosage and schedule [48].

The use of chemotherapy or radiotherapy in patients with operable tumors has not yet been clearly established and widely recommended, although recent studies have shown promising results in the use of adjuvant therapy [49,50]. Kronenfeld et al. reported that 80% of patients with RAAS in their study group responded to neoadjuvant therapy. The patients received either double-agent therapy (doxorubicin/ifosfamide or gemcitabine/docetaxel), or a single agent (paclitaxel). Patients received a median of four cycles of chemotherapy. Response rates were not associated with patient, pathologic, or treatment factors [51]. Another study reported the use of neoadjuvant, accelerated hyperfractionated radiation with concurrent hyperthermia followed by surgical resection for RAAS. Toxicities were modest with an excellent pathologic response and the promise of increased efficacy [52].

5. Conclusion

Due to the established mammary screening with early diagnosis of breast cancer and the preference for breast-conserving procedures with adjuvant radiotherapy, an increase in the incidence of RAAS can be expected. According to the literature, the prognosis of patients with RAAS is unfavorable. An early diagnosis is the cornerstone of RAAS therapy; it requires the collection of a biopsy sample sufficient for valid pathological evaluation including a potential repeat sampling in case of negative histological examination of the primary biopsy. Surgical treatment with a negative resection margin is the most important part of the therapy. The adjuvant chemotherapy did not statistically significantly improve the outcome in local recurrence and survival rate in our cohort in comparison with patients without adjuvant chemotherapy. Neoadjuvant chemotherapy and hyperfractionated radiation with concurrent hyperthermia, however, show promising results. We have confirmed the findings to date on a relatively large sample. However, RAAS continues to be a difficult-to-treat diagnosis.

Statement of the ethics committee

The project for all participating institutions from Slovakia and the Czech Republic was approved by the Ethics Committee of the Masaryk Cancer Institute on November 20, 2018, (2018/3037/MOU).

Funding CZ

This work was supported by the MH CZ – DRO (MMCI, 00209805).

Funding SK

This publication was created thanks to support under the Operational Programme Integrated Infrastructure for the project: Integrative strategy in development of personalized medicine of selected malignant tumors and its impact on quality of life, IMTS: 313011V446, co-financed by the European Regional Development Fund.

Author statement

Jana Mergancová; Conceptualization, Methodology, Writing- Original draft preparation, Writing - Review & Editing.
Anna Lierová; Investigation, Data curation, Visualization.
Oldřich Coufal: Investigation, Supervision, Funding acquisition.
Jan Žatecký; Investigation, Writing - Review & Editing.
Bohuslav Melichar: Investigation, Supervision, Validation.
Ilona Zedníková; Investigation.
Jindřiška Mergancová; Investigation.
Anna Jesenková; Investigation.
Karel Šťastný; Investigation.
Jiří Gatěk: Investigation.
Otakar Kubala: Investigation.
Jiří Prokop: Investigation.
Daniel Dyttert: Investigation.
Marián Karaba: Investigation.
Ivana Schwarzbacherová; Investigation.
Anna Humeňanská; Investigation.
Jindřich Šuk: Investigation.
Michal Valenta: Investigation.
Vladimír Moucha: Investigation.
Lukáš Sákra: Investigation.
Aleš Hlávka: Investigation.
Mária Hácová; Investigation.
Radovan Vojtíšek: Investigation.
Marek Sochor: Investigation.
Tomáš Jirásek: Investigation.
Michaela Zábojníková; Investigation.
Martina Zemanová; Investigation.
Katarína Macháleková; Investigation.
Dominika Rusnáková; Investigation.
Eva Kúdelová; Investigation.
Marek Smolár: Investigation, Writing- Original draft preparation, Writing - Review & Editing, Funding acquisition, Project administration.

Declaration of competing interest

All authors declare no conflict of interest.

References

[1] R. Vojtíšek, Z. Kinkor, J. Fínek, Secondary angiosarcomas after conservation treatment for breast cancers, Klin. Onkol. 24 (5) (2011) 382–388.
[2] J. Yap, P.J. Chuba, R. Thomas, et al., Sarcoma as asecond malignancy after treatment for breast cancer, Int. J. Radiat. Oncol. Biol. Phys. 52 (2002) 1231–1237, https://doi.org/10.1016/s0360-3016(01)02799-7.
[3] A.J.M. Rombouts, J. Huising, N. Hugen, et al., Assessment of radiotherapy-associated angiosarcoma after breast cancer treatment in a Dutch population-based study, JAMA Oncol. 5 (2) (2019) 267–269, https://doi.org/10.1001/jamaoncol.2018.6643.
[4] W.G. Cahan, H.Q. Woodard, N.L. Higinbotham, et al., Sarcoma arising in irradiated bone; report of 11 cases, Cancer 1 (1948) 3–29, https://doi.org/10.1002/1097-0142(194805)1:1<3::aid-cncr2820010103>3.0.co;2-7.
[5] M. Arlen, N.L. Higinbotham, A.G. Huvos, et al., Radiation-induced sarcoma of bone, Cancer 28 (5) (1971 Nov) 1087–1099, https://doi.org/10.1002/1097-0142(1971)28:5<1087::aid-cncr2820280502>3.0.co;2-f.
[6] E.A. Morgan, D.E. Kozono, Q. Wang, et al., Cutaneous radiation-associated angiosarcoma of the breast: poor prognosis in a rare secondary malignancy, Ann. Surg Oncol. 19 (2012) 3801–3808, https://doi.org/10.1245/s10434-012-2563-4.
[7] A. Hui, M. Henderson, D. Speakman, et al., Angiosarcoma of the breast: a difficult surgical challenge, Breast 21 (4) (2012 Aug) 584–589, https://doi.org/10.1016/j.breast.2012.01.001.
[8] Bonito FJP, D. de Almeida Cerejeira, C. Dahlstedt-Ferreira, H. Oliveira Coelho, R. Rosas, Radiation-induced angiosarcoma of the breast: a review, Breast J. 26 (3) (2020 Mar) 458–463, https://doi.org/10.1111/tbj.13504.
[9] E.R. Ghareeb, R. Bhargava, J.A. Vargo, A.V. Florea, S. Beriwal, Primary and radiation-induced breast angiosarcoma: clinicopathologic predictors of outcomes and the impact of adjuvant radiation therapy, Am. J. Clin. Oncol. 39 (5) (2016) 463–467.
[10] J.C. Maddox, H.L. Evans, Angiosarcoma of the skin and soft tissue: a study of forty-four cases, Cancer 48 (8) (1981 Oct 15) 1907–1921, https://doi.org/10.1002/1097-0142(19811015)48:8<1907::aid-cncr2820480832>3.0.co;2-t.
[11] I. Alves, J.C. Marques, Radiation-induced angiosarcoma of the breast: a retrospective analysis of 15 years' experience at an oncology center, Radiol. Bras. 51 (5) (2018 Sep-Oct) 281–286, https://doi.org/10.1590/0100-3984.2017.0129.
[12] R. Abbott, C. Palmieri, Angiosarcoma of the breast following surgery and radiotherapy for breast cancer, Nat. Clin. Pract. Oncol. 5 (12) (2008 Dec) 727–736, https://doi.org/10.1038/ncponc1242.
[13] R.B. Cohen-Hallaleh, H.G. Smith, R.C. Smith, et al., Radiation induced angiosarcoma of the breast: outcomes from a retrospective case series, Clin. Sarcoma Res. 7 (2017 Aug 7) 15, https://doi.org/10.1186/s13569-017-0081-7.

[14] B.J. Barrow, N.A. Janjan, H. Gutman, et al., Role of radiotherapy in sarcoma of the breast—a retrospec-tive review of the M.D. Anderson experience, Radiother. Oncol. 52 (2) (1999 Aug) 173–178, https://doi.org/10.1016/s0167-8140(99)00070-5.

[15] J. Fodor, Z. Orosz, E. Szabó, et al., Angiosarcoma after conservation treatment for breast carcinoma: our experience and a review of the literature, J. Am. Acad. Dermatol. 54 (3) (2006 Mar) 499–504, https://doi.org/10.1016/j.jaad.2005.10.017.

[16] S.B. Edge, D.R. Byrd, C.C. Compton, et al., AJCC:Soft Tissue Sarcoma, Springer, New York, 2010, pp. 291–298.

[17] Bonito FJP, D.A. Cerejeira, C. Dahlstedt-Ferreira, et al., Radiation-induced angiosarcoma of the breast: a review, Breast J. 26 (3) (2020 Mar) 458–463, https://doi.org/10.1111/tbj.13504.

[18] J. Majeski, R.M. Austin, R.H. Fitzgerald, Cutaneous angiosarcoma in an irradiated breast after breast conservation therapy for cancer: association with chronic breast lymphedema, J. Surg. Oncol. 74 (3) (2000 Jul) 208–212, https://doi.org/10.1002/1096-9098(200007)74:3<208::aid-jso10>3.0.co;2-2, discussion 212-3.

[19] C. Marchal, B. Weber, B. de Lafontan, et al., Nine breast angiosarcomas after conservative treatment for breast carcinoma: a survey from French Comprehensive Cancer Centers, Int. J. Radiat. Oncol. Biol. Phys. 44 (1) (1999 Apr 1) 113–119, https://doi.org/10.1016/s0360-3016(98)00537-9.

[20] E. Virgilio, M. Lombardi, D.D. Stefano, et al., Angiosarcoma of the breast: a rare and dismal complication of breast surgery associated with radiation, Am. Surg. 83 (3) (2017 Mar 1) e71–73.

[21] S. Shah, M. Rosa, Radiation-associated angiosarcoma of the breast: clinical and pathologic features, Arch. Pathol. Lab Med. 140 (5) (2016 May) 477–481, https://doi.org/10.5858/arpa.2014-0581-RS.

[22] N. Iga, Y. Endo, A. Fujisawa, et al., Two cases of cutaneous angiosarcoma developed after breast cancer surgery, Case Rep Dermatol 4 (3) (2012 Sep) 247–249, https://doi.org/10.1159/000345559. Epub 2012 Sep 14. PMID: 23275768; PMCID: PMC3531937.

[23] J. Kong, A.D. Shahait, S. Kim, Radiation-induced undifferentiated pleomorphic sarcoma of the breast, at al, BMJ Case Rep. 13 (2) (2020 Feb 10), e232616, https://doi.org/10.1136/bcr-2019-232616. PMID: 32047082; PMCID: PMC7021111.

[24] A. Zafar, P. Neary, G. O'Donoghue, C. Fiuza-Castinieria, A breast surgeon's paranoia pays off: the importance of keen clinical acumen in a case of postradiotherapy breast angiosarcoma, BMJ Case Rep. (2012 Aug 18), https://doi.org/10.1136/bcr-2012-006434, 2012:bcr2012006434.

[25] Y. Farran, O. Padilla, K. Chambers, et al., Atypical presentation of radiation-associated breast angiosarcoma: a case report and review of literature, Am. J. Case Rep. 18 (2017 Dec 18) 1347–1350, https://doi.org/10.12659/ajcr.905157.

[26] J. Cabete, A. Lencastre, A. Fidalgo, et al., Postradiation cutaneous angiosarcoma of the breast: a diagnosis to keep in mind, Breast J. 20 (1) (2014 Jan-Feb) 89–90, https://doi.org/10.1111/tbj.12215.

[27] S.H. Salminen, T. Wiklund, M.M. Sampo, et al., Treatment and prognosis of radiation-associated breast angiosarcoma in a nationwide population, Ann. Surg Oncol. 27 (4) (2020 Apr) 1002–1010, https://doi.org/10.1245/s10434-019-08085-1.

[28] S.H. Salminen, M.M. Sampo, T.O. Böhling, et al., Radiation-associated angiosarcoma of the breast: analysis of diagnostic tools in a registry-based population, Acta Radiol. (2020 Dec 21), 284185120980142, https://doi.org/10.1177/0284185120980142. Epub ahead of print. PMID: 33349000.

[29] M. Ohsawa, N. Naka, Y. Tomita, et al., Use of immunohistochemical procedures in diagnosing angiosarcoma. Evaluation of 98 cases, Cancer 75 (12) (1995 Jun 15) 2867–2874, https://doi.org/10.1002/1097-0142(19950615)75:12<2867::aid-cncr2820751212>3.0.co;2-2874.

[30] J. Rao, J.G. Dekoven, J.D. Beatty, et al., Cutaneous angiosarcoma as a delayed complication of radiation therapy for carcinoma of the breast, J. Am. Acad. Dermatol. 49 (3) (2003 Sep) 532–538, https://doi.org/10.1067/s0190-9622(03)00428-6.

[31] J. Fant, M. Grant, S. May, et al., Angiosarcoma ofthe breast: mammographic, clinical, and pathologic correlation, Breast J. 9 (3) (2003 May-Jun) 252–253, https://doi.org/10.1046/j.1524-4741.2003.09316.x.

[32] T.D. Pencavel, A. Hayas, Breast sarcoma - a review of diagnosis and management, Int. J. Surg. 7 (1) (2009 Feb) 20–23, https://doi.org/10.1016/j.ijsu.2008.12.005.

[33] S. Al-Benna, K. Poggemann, H.U. Steinau, et al., Diagnosis and management of primary breast sarcoma, Breast Cancer Res. Treat. 122 (3) (2010 Aug) 619–626, https://doi.org/10.1007/s10549-010-0915-y.

[34] K.M. Thijssens, R.J. van Ginkel, A.J. Suurmeijer, et al., Radiation-induced sarcoma: a challenge for the surgeon, Ann. Surg Oncol. 12 (3) (2005 Mar) 237–245, https://doi.org/10.1245/ASO.2005.03.041.

[35] Z. Amajoud, A.S. Vertongen, R. Weytens, J. Hauspy, Radiation induced angiosarcoma of the breast: case series and review of the literature, Facts Views Vis Obgyn 10 (4) (2018 Dec) 215–220.

[36] E. Perez-Ruiz, N. Ribelles, A. Sanchez-Muñoz, et al., Response to paclitaxel in a radiotherapy-induced breast angiosarcoma, Acta Oncol. 48 (7) (2009) 1078–1079, https://doi.org/10.1080/02841860902777115.

[37] G.Z. Li, M. Fairweather, J. Wang, et al., Cutaneous radiation-associated breast angiosarcoma: radicality of surgery impacts survival, Ann. Surg. 265 (4) (2017 Apr) 814–820, https://doi.org/10.1097/SLA.0000000000001753.

[38] J.P. Kronenfeld, J.S. Crystal, E.L. Ryon, et al., Clinical outcomes for primary and radiation-associated angiosarcoma of the breast with multimodal treatment: long-term survival is achievable, Cancers 13 (15) (2021 Jul 29) 3814, https://doi.org/10.3390/cancers13153814. PMID: 34359716; PMCID: PMC8345179.

[39] D. Gambini, R. Visintin, E. Locatelli, et al., Paclitaxel-dependent prolonged and persistent complete remission four years from first recurrence of secondary breast angiosarcoma, Tumori 95 (6) (2009 Nov-Dec) 828–831.

[40] N. Penel, B.N. Bui, J.O. Bay, et al., Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study, J. Clin. Oncol. 26 (32) (2008 Nov 10) 5269–5274, https://doi.org/10.1200/JCO.2008.17.3146.

[41] E.S. Casper, R.J. Waltzman, G.K. Schwartz, et al., Phase II trial of paclitaxel in patients with soft-tissue sarcoma, Cancer Invest. 16 (7) (1998) 442–446, https://doi.org/10.3109/07357909809011697.

[42] F. Fata, E. O'Reilly, D. Ilson, et al., Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face, Cancer 86 (10) (1999 Nov 15) 2034–2037.

[43] A. Wallgren, Late effects of radiotherapy in the treatment of breast cancer, Acta Oncol. 31 (2) (1992) 237–242, https://doi.org/10.3109/02841869209088909.

[44] A.L. Depla, C.H. Scharloo-Karels, M.A.A. de Jong, et al., Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review, Eur. J. Cancer 50 (10) (2014 Jul) 1779–1788, https://doi.org/10.1016/j.ejca.2014.03.002.

[45] E.K. Donovan, T. Corbett, J. Vansantvoort, et al., Radical chest wall resection and hyperfractionated accelerated radiotherapy for radiation-associated angiosarcoma of the breast: a safe and effective treatment strategy, Breast J. 24 (3) (2018 May) 245–252, https://doi.org/10.1111/tbj.12886.

[46] J.K. Molitoris, A. Chhabra, J.W. Snider, et al., Intensification of treatment for angiosarcoma of the breast with accelerated hyperfractionated radiation, hyperthermia, and surgical resection, Cureus 9 (6) (2017 Jun 28), e1406, https://doi.org/10.7759/cureus.1406. PMID: 30944783; PMCID: PMC6438684.

[47] M. Notter, E. Stutz, A.R. Thomsen, et al., Radiation-associated angiosarcoma of the breast and chest wall treated with thermography-controlled, contactless wIRA-hyperthermia and hypofractionated Re-irradiation, Cancers 13 (15) (2021 Aug 3) 3911, https://doi.org/10.3390/cancers13153911. PMID: 34359812; PMCID: PMC8345679.

[48] M. Notter, A.R. Thomsen, A.L. Grosu, P. Vaupel, Recommendation of regional hyperthermia in the treatment of breast cancer, Integr. Cancer Ther. 20 (2021 Jan-Dec), https://doi.org/10.1177/1534735420988606, 1534735420988606.

[49] A. Arnaout, D.M. Wedman, S. El-Sayed, et al., Neoadjuvant gemcitabine-taxane chemotherapy for radiation-induced angiosarcoma of the breast: a case report, Breast J. 18 (3) (2012 May-Jun) 276–278, https://doi.org/10.1111/j.1524-4741.2012.01239.x.

[50] Y. Suzuki, K. Taniguchi, M. Hatono, et al., Recurring radiation-induced angiosarcoma of the breast that was treated with paclitaxel chemotherapy: a case report, Surg. Case Rep. 6 (1) (2020 Jan 16) 25, https://doi.org/10.1186/s40792-020-0790-7.

[51] J.P. Kronenfeld, J.S. Crystal, E.L. Ryon, et al., Clinical outcomes for primary and radiation-associated angiosarcoma of the breast with multimodal treatment: long-term survival is achievable, Cancers 13 (15) (2021 Jul 29) 3814, https://doi.org/10.3390/cancers13153814.

[52] J.K. Molitoris, A. Chhabra, J.W. Snider, et al., Intensification of treatment for angiosarcoma of the breast with accelerated hyperfractionated radiation, hyperthermia, and surgical resection, Cureus 9 (6) (2017 Jun 28), e1406, https://doi.org/10.7759/cureus.1406.