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Clinical management of secondary angiosarcoma after breast conservation therapy

Martina Zemanova[a,b,*], *Katarina Machalekova*[c], *Monika Sandorova*[b], *Elena Boljesikova*[b], *Marta Skultetyova*[d], *Juraj Svec*[a], *Andrej Zeman*[e]

[a] *1st Department of Oncology, Faculty of Medicine, Comenius University and St. Elisabeth Cancer Institute, Bratislava, Slovakia*
[b] *Department of Radiation Oncology, St. Elizabeth Cancer Institute, Bratislava, Slovakia*
[c] *Department of Pathology, St. Elizabeth Cancer Institute, Bratislava, Slovakia*
[d] *Department of Clinical Oncology, St. Elizabeth Cancer Institute, Bratislava, Slovakia*
[e] *Department of Nuclear Sciences and Applications, International Atomic Energy Agency, Vienna, Austria*

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ABSTRACT

Aim: The aim of this paper is to summarize the treatment outputs of secondary angiosarcoma after breast conservation therapy at St. Eizabeth Cancer Centre, Slovakia.
Background: Angiosarcoma of the breast is a rare but very aggressive malignant tumor of the vascular endothelium, characterized by rapidly proliferating and extensively infiltrating growth. Breast angiosarcoma may occur de novo, or as a complication of radiation therapy, or chronic lymphedema secondary to axillary lymph node dissection for mammary carcinoma. Radiotherapy in the treatment of breast cancer is associated with an increased risk of subsequent sarcoma.
Materials and methods: Retrospective study of medical records from the cancer databases was done in order to analyze the secondary breast angiosarcoma. This disease is an iatrogenic condition that warrants close follow-up and judicial use of radiotherapy in breast conserving therapy. Therefore, it is more prevalent in cases treated with radiotherapy, occurring especially in or adjacent to the radiation field. Clinical histories and follow-up data of identified patients after breast conservation therapy of invasive breast cancer were reviewed. In addition, a comprehensive literature review on diagnosis and treatment procedures was done in order to summarize state-of-the-art clinical approach.
Results and discussions: Three cases of secondary angiosarcoma after breast conservation therapy (BCT) were identified among 4600 patients treated at St. Elizabeth Cancer Institute during previous 16 years (1995–2011). Secondary breast angiosarcoma was diagnosed in a median period of 11 years following primary radiotherapy, median age at the time of diagnosis was 75 years. Surgical treatment consisted of radical mastectomy. The first patient, a 56-year-old woman received neoadjuvant chemotherapy (docetaxel + gemcitabin), second one (75 year) was treated by radiotherapy (TD 26 Gy, 2 Gy per fraction), since chemotherapy was not indicated. The last patient (80 year) got adjuvant chemotherapy (paclitaxel). Average follow up of the patients was 31 months. As of 31 July 2012, our patients were doing well without evidence of recurrent disease after treatment.

* Corresponding author at: Faculty of Medicine, Comenius University, Bratislava, Slovakia. Tel.: +421 245996810.
E-mail address: mata.zemanova@gmail.com (M. Zemanova).

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Conclusions: Angiosarcoma remains a difficult management problem with poor loco-regional and distal control. In our study, an overall incidence rate of secondary breast angiosarcoma is 0.065%. Although the prognosis for this disease is poor (typical survival period is 14.5–34 months with a 5-year survival rate of approximately 15%), all the three patients treated at our institute are alive and disease-free at the end of reported period. Finally, it is assumed that the use of breast conserving therapy will increase the incidence of post-irradiation angiosarcoma but the small difference in risk of subsequent sarcoma of the breast cancer patients receiving radiotherapy does not suppress its benefit.

1. Background

Angiosarcoma (AS) is a very aggressive malignant tumor of the vascular endothelium, characterized by rapidly proliferating and extensively infiltrating growth and it may occur in any organ of the body. This malignancy can originate in the liver, breast, spleen, bone or heart'; however, it most frequently arises in the skin and soft tissue. Approximately 1–2% of all soft-tissue sarcomas are angiosarcomas, approximately 8% of which arise in the breast.[1,2] In Europe, soft tissue sarcomas have estimated incidence averaging 5/100,000/year.[3] Breast AS may occur de novo or as a complication of radiotherapy (RT) or chronic lymphedema after radical mastectomy for mammary carcinoma (Stewart–Treves Syndrome).[4–6] The frequency of this entity has declined because of the shift to breast conservation therapy for early stage mammary carcinoma in the last 20 years. AS originated in the breast can metastasize via the blood system to the liver, lung, or bone. Both primary and secondary breast angiosarcomas carry a prognosis worse than mammary carcinoma.

Primary AS of the breast typically occurs in younger women without previous history of mammary carcinoma or any associated factor, a median age of onset between 20 and 40 years[7] accounts for 0.04% of all malignant breast tumors.[8] It is usually present as rapidly growing palpable breast mass. Disease free survival rates were reported between 18 and 36 months.[9]

Secondary angiosarcoma is usually found in older women who have undergone breast cancer treatment. The average time between radiation therapy and AS development is 6 years, although several reports indicate this may occur as early as 1–2 years or as late as 41 years after treatment.[10] Postradiation AS was defined by Cahan et al. and modified by Arlen et al. as follows: location in the previous field of radiation, latency of years after radiation therapy, and histologic distinction from the primary neoplasm.[11,12] There are two types: lymphedema-associated cutaneous and postradiation angiosarcomas. Lymphedema-associated cutaneous AS was first described in 1948 by Stewart and Treves, also known as Stewart–Treves syndrome, and it develops on the lymphedematous limb or chest wall after mastectomy and axillary lymph node dissection. Increased use of breast conservation therapy (BCT) and sentinel lymph node sampling has lowered the incidence of treatment-related lymphedema.[13]

Postradiation angiosarcoma generally occurs after BCT and RT and rarely arises in the irradiated chest wall after mastectomy. The first case of secondary angiosarcoma in the skin overlying an irradiated breast was reported in 1981.[14] Since then, approximately 300 cases of post-radiation angiosarcomas of the breast have been reported in English literature. In 2001, a retrospective study conducted by Huang and Mackillop[15] on 194,798 breast cancer patients treated between 1973 and 1995, provided useful clues regarding this relative risk. In this cohort of patients, the age standardized incidence ratios for AS was 26.2 and 2.1 in the RT and non-RT cohort, respectively. The study published in 2005 reported that breast AS has a prevalence ranging between 0.002% and 0.005% per year.[16] A recent study, however, suggests that the incidence may be considerably higher (even more than 0.3%).[17]

AS usually affects the dermis of the breast but occasionally develops in the breast parenchyma. It can initially resemble a bruise, or a raised purplish-red multifocal nodules, eczematous rash, hematoma-like appearance or breast swelling, which may delay the correct diagnosis.

The diagnostic of AS can be delayed due to unclear imaging findings. In many cases, radiographic assistance in making the diagnosis is rather limited. Mammography may reveal skin thickening and ill-defined superficial mass and therefore these findings could be often non-specific. Sonographically, angiosarcomas typically present as a hypervascular, heterogeneous and hyperechoic mass that is associated with disruption of the normal breast architecture, so any dermal lesions may be difficult to differentiate from postradiation skin thickening. MRI seems to be the best option for determination of high-grade angiosarcomas. This is typically used to ascertain lesion extension by showing a rapidly enhancing heterogeneous mass with hemorrhage or blood lakes. An example of diagnostic challenges is a recent publication with summary of imaging findings.[18] The authors reported that nearly 33% of patients with breast angiosarcomas had negative mammograms.

Early and low-grade AS may be subtle; differentiating low-grade type from atypical postradiation vascular lesions may be difficult, because they both represent the low-grade end of the morphologic spectrum of radiation-associated vascular lesions. Classification of vascular tumors according to WHO is described in Table 1. Since angiosarcomas are included within the board category of vascular tumors (Table 1), differential diagnosis is rather complicated and it requires expert histological assessment.[19]

From the histological point of view, the confirmation of the AS diagnosis is normally done by punch and core cut biopsy.

Table 1 – Classification of vascular tumors (WHO).

Reactive and benign vascular tumors	Intermediate grade vascular tumors	Malignant vascular tumors	Tumors of perivascular cells
Capillary haemangiomas Cavernous haemangiomas Epithelioid haemangioma Vascular ectasis Angiomatosis Postradiation atypical vascular lesion	Kaposi's sarcoma Epithelioid haemangioendothelioma	Angiosarcoma	Haemangiopericytoma

Table 2 – Overview of histologic grading of breast angiosarcoma adopted from Donnell et al.[22]

Histological findings	Low grade	Intermediate grade	High grade
Lesion invading breast parenchyma	Present	Present	Present
Hyperchromatic endothelial cells	Present	Present	Present
Well-formed anastomosing	Entirely	Largely	Scattered
Endothelial tufting	Minimal	Present	Prominent
Papillary formations	Absent	Focally present	Present
Solid and spindle cell foci	Absent	Absent or minimal	Present
Mitoses	Rare or absent	Present in papillary area	Numerous
Infarction and "blood lakes"	Absent	Absent	Present
Necrosis	Absent	Absent	Present

A low-grade AS exhibits an indolent, smoldering clinical similar to that of benign atypical vascular lesion. However, local recurrences of low grade AS have been published.[20,21] High-grade AS is a very aggressive tumor which has a poorly differentiated histology and, therefore, rather negative prognostic indicator for patients. AS has a more aggressive behavior than other histological types of cancer, while malignant phyllodes tumors (i.e. those having >10 mitoses/10 high power fields and marked stromal overgrowth) have the metastatic rate of 20–30%. Often, high-grade AS may be mistaken for high-grade mammary carcinoma. Nevertheless, Rosen's method for grading breast AS is easy to implement and correlates well with clinical outcome.[22] Moreover, low grade AS may transform into the high-grade type. The histological grading of mammary AS is shown in Table 2 and it is important to emphasize that normally 60% of tumors have high histological grade with an infiltrative margin.[23,24]

AS typically express endothelial markers including von Willebrand factor, CD 34, CD 31, Ulex europaeus agglutinin 1, and vascular endothelial growth factor (VEGF). Immunohistochemistry is therefore important in confirming the diagnosis. Von Willebrand factor, U europaeus Agglutinin 1, and CD 31 are the most useful markers in poorly differentiated cases.[25] In one study, more than 89% of cells in two of the three postradiation angiosarcoma cases were CD117-positive (expression of the tyrosine kinase receptor KIT).[26] However, progressive tumors dedifferentiation may lead to the loss of these markers. The absence of melanocytic markers (S100), human melanoma black-45, and melanoma antigen can help distinguish angiosarcoma from melanoma.

2. Patients and methods

A retrospective analysis of the breast carcinoma and sarcoma databases was done at St. Elisabeth Cancer Institute. From January 1995 to December 2011, approximately 4600 patients were treated for breast tumors. Clinical and pathological factors such as age, mode of presentation, diagnostic and treatment modalities, surgical pathology, loco-regional recurrence and survival rates were reviewed. Based on the database records, only 3 patients were identified as having postradiation AS of the breast. These cases were included and analyzed in the framework of this study. All important details of patients treated by the breast conservation therapy (BCT) for invasive breast cancer (including diagnosis and treatment procedures of secondary angiosarcoma) are shortly described in the following text.

Patient 1: A 44-year-old premenopausal woman was treated for a T1N1M0 (stage IIA) invasive ductal carcinoma (grade 2, l.sin (left side breast)) with quadrantectomy. The axillary dissection (in total 11 lymph nodes, one node was positive with metastasis) and the surgery was performed on January 27, 1998. The size of the tumor was 20 mm and there was negative surgical margin. All investigated oncological markers were negative (CEA, CA 15–3, TPS). The chemotherapy was administrated before (4× anthracycline) and after (2× anthracycline) radiotherapy. Postoperative adjuvant radiotherapy with TD 46.0 Gy (2 Gy per fraction, Co-60) followed by a 10.0 Gy electron boost to the tumor bed was completed in July 1998. Thereafter, Tamoxifen was prescribed (5 years). Only limited post radiation dermatitis (stage I) was observed and there was no history of breast or visible radiation effects.

The patient has no objective problems during a period of 12-years after BCT. She did well until next regular check-up which took place in July 2010. There was no indication of recurrence, although the patient reported local pain in the area of treated breast. Standard diagnostic procedure by mammography (MMG) and ultrasonography (USG) was completed and there was no sign for loco-regional relapse. All investigated oncological markers were also negative. However, two weeks later, the patient claimed intensive pain in the left axilla and arm. Although the pain was declining in this area during next days, further complications occurred, specifically

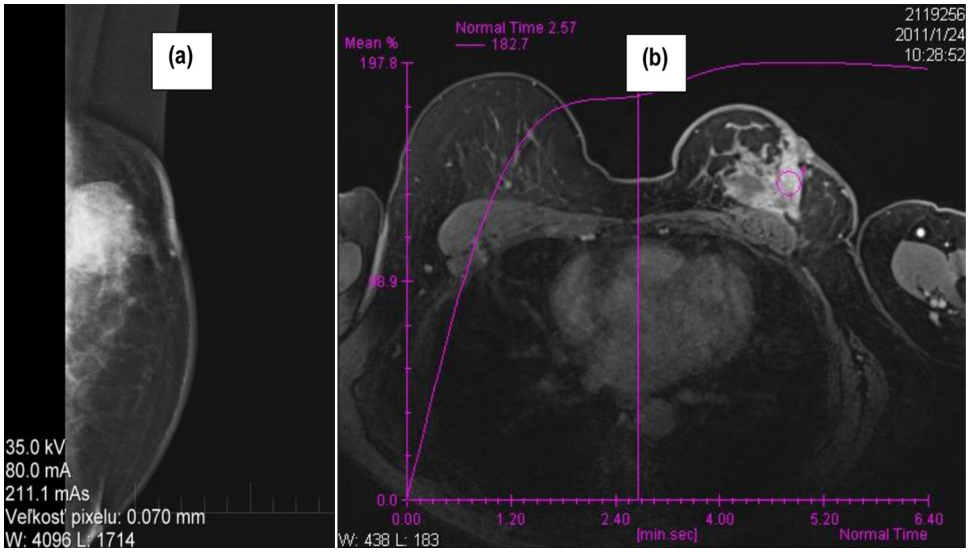

Fig. 1 – Patient 1 (a) mammography of the left breast – MLO projection – increased density of fibroglandular tissue with focal appearance in the upper quadrant of the left breast, (b) MRI of the breast-dynamic contrast enhanced study – markly enhanced infiltration with retractive changes and middle to high proliferating activity.

an inflammation of mammilla and areola. She was treated for suspect inflammation by standard antibiotics. The pain occurred again and she first noted a persistent "red-ring" decoration of areola. A few days later, the patient reported further induration of the central quadrant directly behind areola. Based on anamnesis, there was a suspicion for mastitis (initial phase). Further investigation by the percutaneous aspiration biopsy (PAB) was done in July 2010. This result gave an indication for a local recurrence. Thereafter, local skin excision cutis was completed in order to identify an origin of the induration, however, the finding was negative. Nevertheless, due to observed flat infiltration (34 mm × 22 mm), a MRI was done on August 16, 2010. The MRI described some indication for a new proliferated infiltration between the central and lower median quadrant with further induration of the skin, deformation of affected breast and retraction of its mammilla. Core-cut biopsy performed after MRI examination did not determine any neoplastic changes, however, on the edge of the specimen inflammatory mesenchymal cellulization was increased. Recommended pathological confirmation of the supraclavicular lymph node and PET examination were not performed, because the patient decided to undergo antibiothical treatment by her family doctor. This treatment was without any therapeutical effect. Due to pending complications with no improvement after conventional treatment, in January 2011, the patient came to the oncological centre for further investigation. Immediately, mammography and ultrasound examinations were performed. The outputs of these modalities excluded inflammatory mastitis and indicated possible tumorous changes of mastitis carcinomatosa. Very significant progress in the skin induration was confirmed by MRI. Infiltrated region almost doubled its size (60 mm × 40 mm) from the previous control. Finally, high grade angiosarcoma was confirmed based on additional core-cut biopsy (Fig. 1).

Pathological findings confirmed the inter-anastomosing vascular channels which were intermingled with solid endothelial and spindle cell areas than showed necrotic foci and numerous mitoses. Grade III (poorly differentiated) angiosarcoma was diagnosed. In this particular case, more than 50% of the total neoplastic area was composed of solid and spindle cell components without evident vascular channels (Fig. 2). From January to March, the patient received neoadjuvant chemotherapy (3 cycles of combination Docetaxel 150 mg and Gemcitabin 2000 mg). After chemotherapy a simple left mastectomy was performed. Pathological examination of a mastectomy specimen revealed satisfactory post therapeutic response and only a minimal residual angiosarcoma population was present. Regressive and reparative changes were prevailing. Chemotherapy of further 3 cycles in the previous combination was applied. Chemotherapy treatment was ended on June 22, 2011, 6 month after beginning of the treatment. Further investigated control mammography, ultrasound, MRI of the breast, CT of brain, chest and abdomen were with negative results in terms of distant metastases.

Patient 2: A 69-year-old women, had a T1N0M0 invasive ductal carcinoma of the breast treated with lumpectomy. The size of tumor was 10 mm. The postoperative RT to 46.0 Gy (2 Gy per fraction) was delivered. It was followed by a 10.0 Gy boost to the tumor bed in July 2004. There was no history of breast or arm edema or visible radiation late effect such as teleangiectasia or fibrosis. Similarly like case 1 and 2, this patient also got hormonal therapy during 5 years period.

This patient had no significant problems during following 76 months, only sensitization of the treated breast, mild pain and discreet lymphoedema was reported one year after BCT. However, in November 2010, she had a sudden onset of swelling over the breast with several "port wine" lesions developed in the skin of the treated breast. During the next week, the lesions appeared to decrease in size and fade, suggesting resolution of a traumatic etiology to the following clinician. Nine week later, however, there were well-defined,

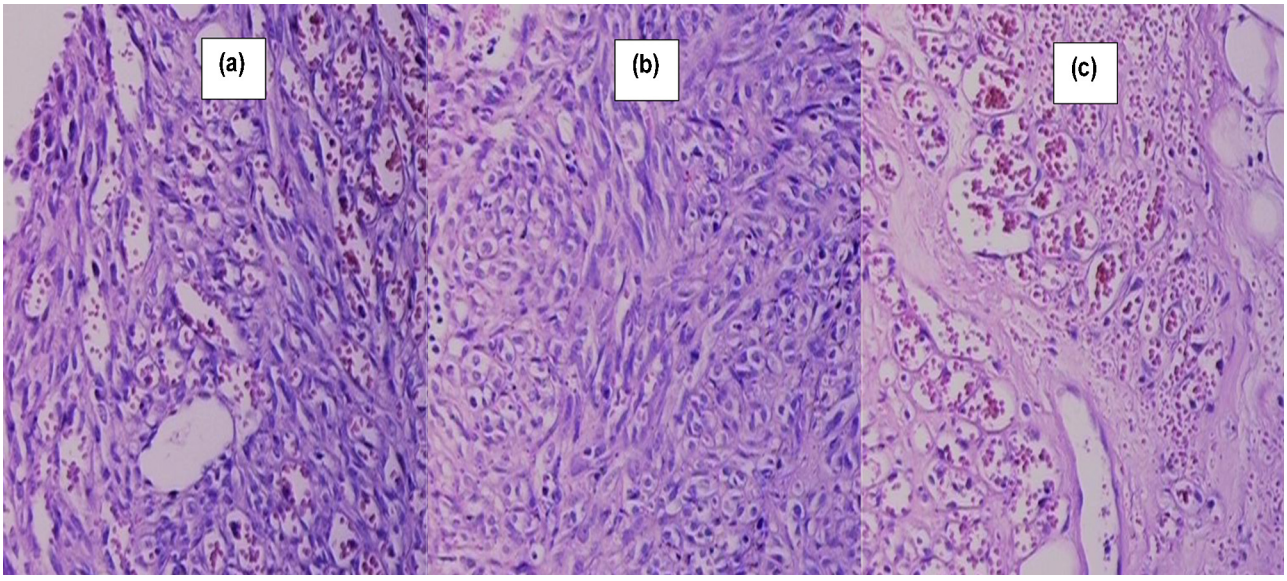

Fig. 2 – Patient 1, core-cut biopsy (a) high-grade angiosarcoma, composed of neoplastic spindle cell population arranged in cohesive clusters (distinct vascular spaces are formed and covered by hobnail cells), (b) hypercellular part of the angiosarcoma, comprising of spindle and epitheloid cells with whorl formations and tiny capillaries, (c) breast amputation: residual vascular spaces filled with erythrocytes and covered by atypical endothelial cells, placed in a hyaline stoma- this represents the sole residual neoplastic formations of the previously diagnosed angiosarcoma (all pictures hematoxylin – eosin stain, original magnification 200×).

a little purple–red, macular and papular skin lesions. USG confirmed hematoma-like appearance, with small petechial lesions. A biopsy specimen from April 24, 2011 was consistent with atypical vascular proliferation, but suspicious for angiosarcoma (tumor size was 22 mm × 20 mm). A total mastectomy was completed on May 12, 2011 and it revealed high-grade AS extensively involving the skin, focally involving the breast parenchyma (Fig. 4). After surgery, the patient received 8 cycles of adjuvant chemotherapy (paclitaxel 130 mg weekly). Chemotherapy was ended three months later for complications which were neutropenia Gr.II leucopenia Gr.II and polyneuropathy.

Patient 3: A 70-year-old woman was treated for a left breast T1N0M0 (AJCC stage I) invasive lobular carcinoma with lumpectomy. The size of the tumor was 17 mm with negative surgical margins. The surgery was followed by postoperative RT (46.0 Gy, 2 Gy per fraction) and a subsequent 10.0 Gy electron boost to the tumor bed. The treatment was completed in October 1995. There was a history of discreet arm edema one year after RT. Standard hormonal therapy was followed (Tamoxifen for 5 years). Only limited post radiation dermatitis (stage I) was observed. Comparably to case 1, there was no evidence of other postradiation complications (edema, teleangiectasia or fibrosis).

The patient did well until December 2005 (10 years after BCT), when she first noted a painful area and erythema of the left arm and breast which occurred shortly after influenza vaccination. She was treated for dermatitis with no improvement. Six weeks later she noted a bruise on the breast and the size of the lesion increased slightly, and small lumps were noted under the scar. In January 2006, USG was done for diagnosis of the root cause of pending problems. Due to unclear sonographic findings, a cytological examination by PAB was done. This indicated possible local recurrence at the site of the original breast tumor. Further investigation was done by MRI which showed an intraparenchymal mass (75 mm × 25 mm). A biopsy specimen was taken and analyzed in February 2006 and angiosarcoma was confirmed. A total mastectomy on April 7, 2006 revealed high-grade angiosarcoma (grade 3, see Fig. 3) involving only breast parenchyma without infiltration into the skin and measuring 80 mm in diameter. Total mastectomy was done with a negative margin (more than 20 mm). Chemotherapy was planned but not applied for cardiac contra-indication. Subsequently, the patient was treated with external RT to the chest wall with low-energy (6.0 MeV) electrons one fraction daily to a total dose of 26.0 Gy (2 Gy per fraction). The chemotherapy was not indicated and treatment was completed on June 9, 2006. As of July 31, 2012, the patient was doing well, without evidence of recurrent disease after the treatment.

3. Results and discussion

Nowadays, breast conservation therapy with wide local excision and postoperative RT is the standard treatment of early stage breast carcinomas. According to previously published data, RT reduces local disease recurrence, but significant side effects exist from mild dermatitis to angiosarcoma.[27,28] However, with the increasing diagnosis of early breast cancers, amenable to breast conservation, an increase in the incidence of secondary AS may be expected. The rarity of the disease and the unspecific clinical, histological and radiological

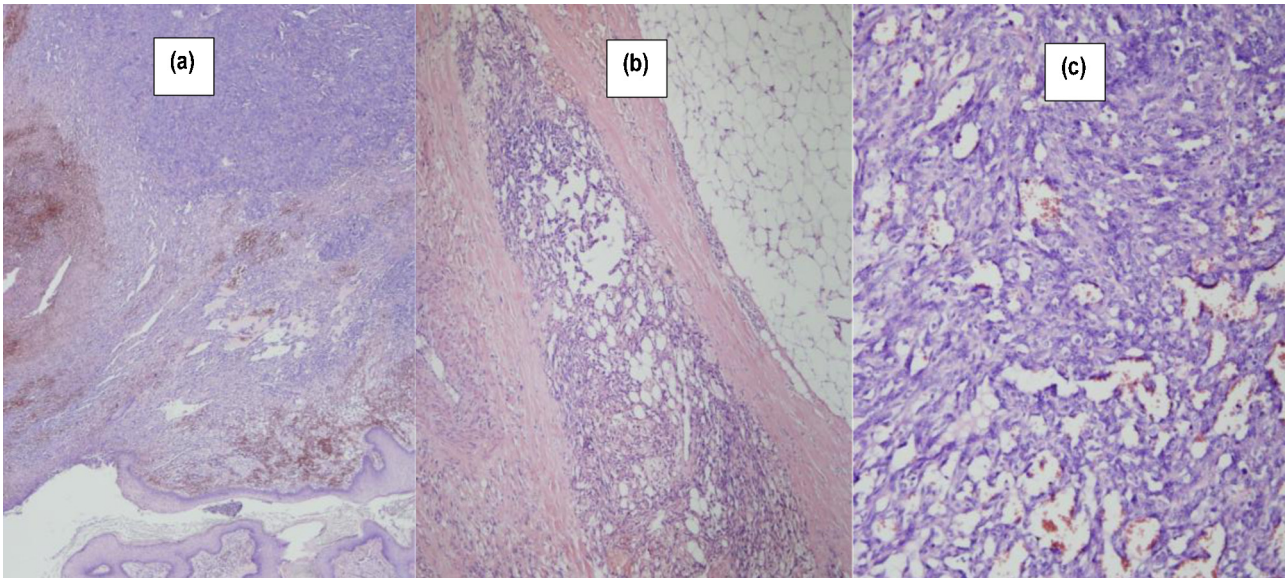

Fig. 3 – Patient 2 (a) angiosarcoma of the breast: infiltration of the skin with high-grade spindle cell sarcoma with forming of vascular spaces, prominent areas of hemorrhage and superficial ulceration (hematoxylin – eosin stain, magnification 20×), (b) invasion of the tumor to the deep adipose tissue of the breast (hematoxylin – eosin stain, magnification 100×), (c) high-grade spindle cell sarcoma with slit-like spaces lined with atypical hobnail cells (hematoxylin – eosin stain, magnification 200×).

features may significantly delay its diagnosis. The treatment approaches are briefly discussed in the following paragraphs.

Generally, as regards the therapy, it is important to underline that AS treatment has to be planned by a multidisciplinary team. Normally, surgery is the best way to achieve the local control of this aggressive malignancy. However, currently there are no standard guidelines concerning surgical margin. Obtaining negative surgical margins is more important than the type of surgery.[29,30] The standard surgical procedure is mastectomy with negative margins. It is recommended that this should be carried out in a sarcoma specialist unit especially if the tumor is beyond the confines of the remaining breast tissue or encroaching the chest wall. However, in case of rapid growth after clinical manifestation, the tumor could be inoperable. For locally advanced inoperable or metastatic disease, chemotherapy is the pillar of treatment. Grade and surgical margin status are important prognostic determinants also in cases of post-irradiation sarcomas.[31]

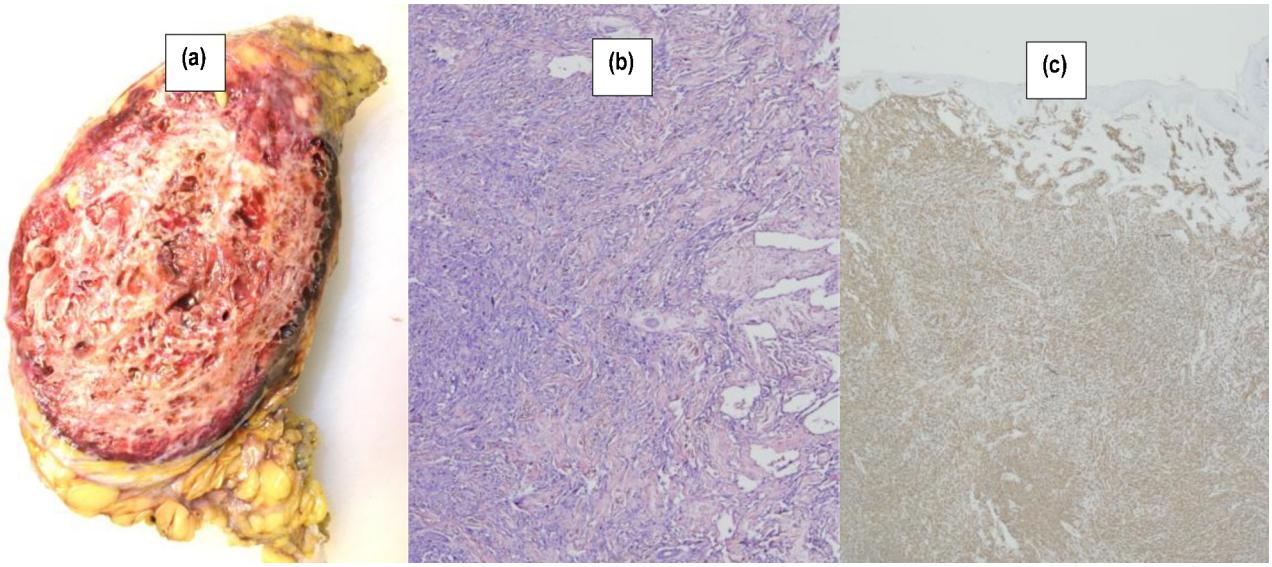

Fig. 4 – Patient 3 (a) gross view of the breast angiosarcoma with cystic spaces and areas of heamorrhage on cut surface, (b) detailed picture of the border between hypercellular spindle cell component of the tumor and slit-like vascular spaces forming (hematoxylin – eosin stain, magnification 100×), (c) Immunohistochemical stain of CD31 in high-grade angiosarcoma of the breast (CD31 stain, magnification 20×).

Nowadays, the role of chemotherapy has not been fully standardized, as usually only short-lived responses are reported in the literature. Treatment has been included in management guidelines for other soft-tissue sarcomas, such as those published by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN). Despite a strong need for systemic therapies, the rarity of angiosarcoma represents a major limitation to randomized trials and therefore only few prospective clinical studies are available. Most data are represented by retrospective case series analyses or case reports, all suggesting that among soft tissue sarcomas, angiosarcoma appears to be more sensitive to cytotoxic chemotherapy.[32] Angiosarcomas are particularly sensitive to taxanes and liposomal doxorubicin.[33,34] This appears to be true also for breast AS given that some reports have confirmed responses to these agents.[35] As a result, weekly paclitaxel or liposomal doxorubicin may be considered as valid alternatives to standard anthracyclines plus/minus ifosfamide treatment for this particular histology in view of their manageable adverse effect profile. In a phase II trial, paclitaxel has shown encouraging results in unresectable angiosarcomas.[36,37] Even if the response rate of angiosarcoma to these treatments is high compared with other sarcomas, their dose-limiting toxic effects (mostly cardiac and neurological) do not allow to prolong these therapies for >6–7 months in most cases.[38] In addition, secondary resistance after response is frequent. Moreover, the combination of anthracyclines plus ifosfamide can be difficult to administer in many angiosarcoma patients, given their age and PS. Postradiation secondary angiosarcoma patients can be pretreated with anthracycline-based chemotherapy, with a limited bone marrow reserve, and they are likely to carry DNA repair mechanism defects that can underlie increased chemoresistance to cytotoxics like the alkylating agent. In particular, the response rate to doxorubicin – the standard frontline chemotherapy for advanced sarcoma – as a single agent or in combination, is reported to the range between 40% and 65%.[39,40] Besides anthracyclines, taxanes can be active, both as single agents and in combination with gemcitabine or with anthracyclines, with response rates between 20% and 65%.[41,42]. Responses to taxanes alone or in combination with gemcitabine are well documented. In fact, tolerability of gemcitabine plus docetaxel is fair, with less cardiac toxicity compared with anthracyclines but still carrying a significant incidence of neutropenia and thrombocytopenia.[43,44] Only very few data are available on gemcitabine as a single agent. For these reasons, gemcitabine seems to be a very promising therapeutic option.[45,46] Among new angiogenesis-related molecules, the activity of sorafenib, sunitinib, bevacizumab, and thalidomide has been reported, with response rates of approximately 15%.[47–49]

Currently, most clinicians are reluctant to include radiation treatment in the therapy plan because of surrounding healthy tissue radiation limits even years after initial RT. The rationale underlying the use of hyperfractionated RT is that breast angiosarcomas have a high growth rate, making them more likely to repopulate between daily fractions of radiotherapy. The use of multiple daily fractions might, therefore, prevent repopulation from occurring. In 2002, promising results of neoadjuvant hyperfractionated RT in conjunction with surgery for secondary AS were reported.[50] The authors reported 3 patients who were treated initially with radical surgery for AS, but extensive recurrences were noted within 1 to 2 months after surgery. Because of the extremely rapid growth noted before and after surgery, hyperfractionated RT was used to a total dose of 60 Gy (1.5 Gy per fraction twice daily, with a 6-hour interval between the daily fractions). The three patients underwent planned resection after RT, and none of the specimens demonstrated any evidence of AS. The patients were alive without any recurrent disease 22–39 months after treatment. Another, retrospective study of 13 patients, who received hyperfractionated accelerated radiotherapy, showed that this fractionation regimen is well tolerated and provides local control in nearly 60% of patients (three fractions of 1 Gy per day, surgery before and after radiation). Their 5-year overall survival was 86%.[51] Hyperfractionated RT seems effective for the treatment of postirradiation AS and warrants further investigation. Although angiosarcoma is more prevalent in cases treated with radiotherapy, occurring especially in or adjacent to the radiation field, this limited risk of subsequent secondary malignancies does not suppress the benefit of this modality. Due to the rarity of the condition, patients are often present late in their path (course) of follow up and disease progression is rapid. The median survival period is 14.5–34 months with a 5-year survival rate of approximately 15%.[52]

In our study, 3 cases of high-grade secondary angiosarcoma of the breast were diagnosed and successfully treated at St. Elizabeth Cancer Institute. The median age of primary breast cancer was 57 years (range 44–70 years). All patients, after BCT, received external beam irradiation with a median radiation dose of 50 Gy. Only limited post radiation dermatitis (stage I) was observed and there was no history of breast or arm edema or other visible radiation effects such as teleangiectasis or fibrosis. The median age at diagnosis of secondary AS after BCT was 67 years (range 56–75 years), with a median latent period of 9 years (range 6–12 years). The presentation of AS was varied and included purple cutaneous discoloration, eczematous rash, hematoma like appearance, and breast swelling. There were no cases of regional lymphadenopathy. Treated patients had preoperative staging investigations before surgery. Tumor was extensively involving the breast parenchyma (1 case) and skin and breast parenchyma (2 cases) with varying degrees of nuclear atypia, hyperchromatic nuclei, large nucleoli, and frequent mitoses, “blood lakes” which represent hemorrhage into surrounding stroma. Tumor grade is also known to be an important prognostic factor in cancer survival, however, it is perhaps not so important in radiation induced angiosarcoma (RA), because all our lesions are regarded as high grade. In our analysis, all three patients underwent radical mastectomy with clear margins (more than 20 mm) without axillary lymphadenectomy. The first patient was treated with neoadjuvant and adjuvant chemotherapy (docetaxel and doxorubicin). The second patient received chemotherapy with paclitaxel (neutropenia grade II occurred). The third patient received adjuvant radiotherapy (chemotherapy was not indicated due to cardiotoxicity and age), and only radiodermatitis grade I was presented after RT. Follow up evaluation after diagnosis of AS ranged from 20 to 79 months, with a median of 22 months.

Disease free period after treatment AS ranged from 9 to 73 months, with a median of 13 months. As of July 31, 2012, our three patients were doing well, control mammography, ultrasound, MRI of the breast and brain, chest and abdomen were with negative results in terms of distant metastases after treatment. Although the follow up of our patients is rather short, it is very important to report the clinical data and experience in order to share best-practice which would help obtain the earliest possible diagnosis of this rare but very aggressive malignancy. The multimodal therapeutic approach to this aggressive disease and comparison of clinical experiences from other cancer institutes will be essential for further improvement of early stage diagnostics and treatment approaches.

In our study, the incidence of angiosarcoma was 0.065% which corresponds to clinical data published recently. The median age of diagnosis secondary AS after BCT was 75 years (range 56–80 years), a latent period of 10 years (range 6–12 years) and the TNM classification for primary breast carcinoma was T1N0-1 (only one out of eleven nodes was detected with micrometastasis in one case). Here comes the question about radiotherapy outcome in the elderly presenting with low-risk breast carcinoma? In a large-scale study of Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Oncology Group,[53] 636 women who were 70 years of age or older and who had clinical T1N0M0, stage I, according to the tumor–node–metastasis classification, estrogen receptor-positive breast carcinoma were randomly assigned to receive postoperatively tamoxifen plus radiation therapy or tamoxifen alone. The only significant difference between the two groups was found in the rate of LR or regional recurrence at 5 years (1% in the group given tamoxifen plus irradiation and 4% in patients given tamoxifen alone, $P < 0.001$). There were no significant differences between the two groups with regard to 5-year rates of overall survival. The authors concluded that lumpectomy plus adjuvant therapy with tamoxifen alone is a realistic choice for the treatment of women aged 70 years or older who have early, estrogen receptor-positive breast cancer. In summary, while the effectiveness of radiation therapy in reducing LR after BCS in unselected patients with early stage invasive breast cancer has been repeatedly substantiated, the ratio between benefits and risks of adjuvant radiotherapy in highly selected, low-risk breast cancer patients still remains to be explored prospectively at a large scale.[54]

Finally, it is important to emphasize that much of the published data on these rare tumors are based on case series, which causes difficulty in interpretation of results, because reporting may be selective, datasets incomplete, and treatment approaches diverse, even within the same institution.

4. Conclusions

Generally, the prognosis for angiosarcoma of the breast is rather poor. Even though the association of the BCT and secondary AS is clear, it is frequently missed. The patients often present late in their course of follow-up and disease progression is rapid. Diagnosis of AS can sometimes be troublesome, the histological aspect may vary in the same tumor from that of a highly undifferentiated carcinoma to a form of benign vascular hyperplasia. Therefore, the diagnosis may by incorrect, particularly when only a small biopsy is taken (as in the case presented here).

Breast conservation therapy with wide local excision and postoperative RT is the standard treatment of early stage breast carcinomas. According to previously published data, RT reduces local disease recurrence, but significant side effects exist from mild dermatitis to angiosarcoma. However, with the increasing diagnosis of early breast cancers, amenable to breast conservation, an increase in the incidence of secondary AS may be expected. Angiosarcoma is more prevalent in cases treated with radiotherapy, occurring especially in or adjacent to the radiation field. With increasing use of breast conservation therapy for breast cancer, number of reports on postradiation angiosarcomas has increased. But the small difference in the risk of subsequent sarcoma for breast cancer patients receiving radiotherapy does not supersede the benefit of radiotherapy.

In order to highlight this aggressive condition, rational clinical aspects of presentation, treatment and outcomes should be reported by clinicians as often as possible. Finally, early stage diagnosis and appropriate combination of surgery, chemotherapy and/or radiotherapy can improve a local control significantly. In our study we presented and summarized the clinical experience on combination of different modalities done on individual basis in respect of specific patients' conditions which brought successful results in the treatment procedures.

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Conflict of interest

None declared.

REFERENCES

1. Abbott R, Palmieri C. Angiosarcoma of the breast following surgery and radiotherapy for breast cancer. *Nat Clin Pract Oncol* 2008;**5**(12):727–36.
2. Folpe AL, Gowen AM. Malignant vascular tumours. In: Weiss SW, Goldblum JR, editors. *Enzinger and Weiss's Soft Tissue Tumors*. St. Louis: Mosby; 2001. p. 917–57.
3. Casali PG, Blay JY. Soft tissue sarcomas: ESMO clinical practice guidelines for diagnosis, treatment and follow up. *Ann Oncol* 2010;**21**(5):198–203.
4. Roy P, Clark MA, Thomas JM. Stewart–Treves syndrome-treatment and outcome in six patients from a single centre. *Eur J Surg Oncol* 2004;**30**:982–6.
5. Plogar C, Orosz Z, Fodor J. Is postradiation angiosarcoma of the breast so rare and does breast lymphedema contribute to its development? *J Surg Oncol* 2001;**76**:239–41.
6. Stewart FW, Treves N. Lymphangiosarcoma in post-mastectomy lymphedema: a report of six cases in elephantiasis chirurgica. *Cancer* 1948;**1**:64–81.

7. Xiao YW, Jakowski J, Tawfik O, Thomas P, Fan F. Angiosarcoma of the breast: a clinopathologic analysis of cases from the last 10 years. *Ann Diagn Pathol* 2009;**13**:147–50.
8. Kiluk JV, Yeh KA. Primary angiosarcoma of the breast. *Breast J* 2005;**11**:115–23.
9. Blanchard DK, Reynolds CA, Grant CS, Donohue JH. Primary nonphylloides breast sarcomas. *Am J Surg* 2003;**186**:359–61.
10. Billings SD, McKenney JK, Folpe AL, Hardcare MC, Weis SW. Cutaneous angiosarcoma following breast-conserving surgery and radiation: an analysis of 27 cases. *Am J Surg Pathol* 2004;**28**:781–8.
11. Cahan WG, Woodward HQ, Higinbotham NL, et al. Sarcoma arising in irradiated bone: report of eleven cases. *Cancer* 1948;**1**:3–29.
12. Arlen M, Higinbotham NL, Huvos AG, et al. Radiation-induced sarcoma of bone. *Cancer* 1971;**28**:1087–99.
13. West JQ, Qureshi A, West JE, et al. Risk of angiosarcoma following breast conservation: a clinical alert. *Breast J* 2005;**11**:115–23.
14. Maddox JC, Evans HL. Angiosarcoma of the skin and soft tissue: a study of forty-four cases. *Cancer* 1981;**48**:1907–21.
15. Huang J, Mackillop WJ. Increased risk of soft tissue sarcomas after radiotherapy in women with breast carcinoma. *Cancer* 2001;**92**:172–80.
16. Luini A, Gatti G, Galimberti V, et al. Conservative treatment of breast cancer: its evolution. *Breast Cancer Res Treat* 2005;**94**:195–8.
17. West JG, Qureshi A, West JE, et al. Risk of angiosarcoma following breast conservation: a clinical alert. *Breast J* 2005;**11**:115–23.
18. Liberman L, Dershaw DD, Kaufman RJ, Rosen PP. Angiosarcoma of the breast. *Radiology* 1992;**183**:649–54.
19. Young RJ, Brown NJ, Reed MW, Hughes D, Woll P. Angiosarcoma. *Lancet Oncol* 2010;**11**:983–91.
20. Monroe AT, Feigenberg SJ, Mendenhall NP. Angiosarcoma after breast-conserving therapy. *Cancer* 2003;**97**:1832–40.
21. Fineberg S, Rosen PP. Cutaneus Angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. *Am J Clin Pathol* 1994;**102**:757–63.
22. Donnell RM, Rosen PP, Lieberman PH, et al. Angiosarcoma and other vascular tumors of the breast: pathologic analysis as a guide to prognosis. *Am J Surg Pathol* 1981;**5**:629–42.
23. Brenn T, Fletcher CD. Postradiation vascular proliferations: an increasing problem. *Histopathology* 2006;**48**(1):106–14.
24. Vorburger SA, Xing Y, Hunt KK, et al. Angiosarcoma of the breast. *Cancer* 2005;**104**:2682–8.
25. Ohsawa M, Naka N, Tomita Y, Kawamori D, Kanno H, Aozasa K. Use of immunohistochemical procedures in diagnosis angiosarcoma: evaluation of 98 cases. *Cancer* 1995;**75**:2867–74.
26. Komdeur R, Hoekstra HJ, Molenaar WM, et al. Clinopathologic assessment of radiation sacromas: KIT as a potential treatment target. *Clin Cancer Res* 2003;**9**:2926–32.
27. Hui A, Henderson M, Speakman D, Skandarajah A. Angiosarcoma of the breast: a difficult surgical challenge. *Breast* 2012;**30**:1–6.
28. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-year follow-up of a randomized trial comparing total mastectomy,lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347**:1233–41.
29. Lindford A, Bohling T, Vaalavirta L, Tenhunene M, Jahkola T, Tukiainen E. Surgical management of radiation-associated cutaneous breast angiosarcoma. *J Plast Reconstruct Aesthetic Surg* 2011;**64**:1036–42.
30. Al-Benna S, Poggemann K, Steinau H-U, Steinstraesser L. Diagnosis and management of primary breast sarcoma. *Breast Cancer Res Treat* 2010;**122**(3):619–26.
31. Cha C, Antonescu CR, Quan ML, Maru S, Brennan MF. Long-term results with resection of radiation-induced soft tissue sarcomas. *Ann Surg* 2004;**239**:903–10.
32. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcomas. *Lancet* 2010;**11**:983–91.
33. Penel N, Bui NB, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. *J Clin Oncol* 2008;**26**(32):5269–74.
34. Mano MS, Fraser G, Kerr J, et al. Radiation-induced angiosarcoma of breast shows major response to docetaxel after failure of anthracycline-based chemotherapy. *Breast* 2006;**15**(1):117–8.
35. Perez-Ruiz E, Ribelles N, Sanches-Munoz A, Roman A, Marquez A. Response to paclitaxel in a radiotherapy-induced breast angiosarcoma. *Acta Oncol* 2009;**48**(7):1078–9.
36. Voutsadakis IA, Zaman K, Leyvraz S. Breast sarcomas: current and future perspectives. *Breast* 2011;**20**(3): 199–204.
37. Fayette J, Martin E, Piperno-Neuman S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behaviour depending on primary site: a retrospective study of 161 cases. *Ann Oncol* 2007;**18**:2030–6.
38. Nakamura R, Nagashima T, Sakakibara M, et al. Angiosarcoma arising in the breast following breast-conserving surgery with radiation for breast carcinoma. *Breast Cancer* 2007;**14**:245–9.
39. Budd GT. Management of angiosarcoma. *Cur Oncol Rep* 2002;**4**:515–9.
40. Fury MG, Antonescu CR, Van Zee KJ, et al. A 14-year retrospective review of angiosarcoma: clinical characteristics, prognostic factors, and treatment outcomes with surgery and chemotherapy. *Cancer J* 2005;**11**:241–7.
41. Schlemmer M, Reichardt P, Verweij J, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of EORTC soft tissue and bone sarcoma group. *Eur J Cancer* 2008;**44**:2433–6.
42. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer* 2005;**104**:361–6.
43. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. *J Clin Oncol* 2002;**20**:2824–31.
44. Maki RG, Wathen JK, Patel SR, et al., for SARC, the Sarcoma Alliance for Research through Collaboration. Randomized phase II study of gemcitabine and docetaxel versus gemcitabine alone in patients with metastatic soft-tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. *J Clin Oncol* 2007;**25**:2755–63.
45. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian rare cancer network. *Ann Oncol* 2012;**23**(2):501–8.
46. Dileo P, Morgan JA, Zahrieh D, et al. Gemcitabine and vinorelbine combination chemotherapy for patients with advanced soft tissue sarcomas. *Cancer* 2007;**109**: 1863–9.
47. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patientswith metastatic or recurrent sarcomas. *J Clin Oncol* 2009;**27**:3133–40.
48. George S, Merriam P, Maki RG, et al. Multicenter phase II trial of sunitinib in thetreatment of nongastrointestinal stromal tumor sarcomas. *J Clin Oncol* 2009;**27**:3154–60.
49. Raina V, Sengar M, Shukla NK, et al. Complete response from thalidomide in angiosarcoma after treatment of breast cancer. *J Clin Oncol* 2007;**25**:900–1.
50. Feigenberg SJ, Mendehall NP, Reith JD, Ward JR, Copeland EM. Angiosarcoma after breast- conserving therapy: experience

with hyperfractionated radiothereapy. *Int J Rad Oncol Biol Phys* 2002;**52**(3):620–6.
51. Palta M, Morris CG, Grobmyer SR, Copeland EM, Mendenhall NP. Angiosarcoma after breast-conserving therapy. *Cancer* 2010;**116**(8):1872–8.
52. Marchal C, Weber B, De Lafontan B, 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**:113–9.
53. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;**351**:971–7.
54. Bernier J. Potential risks and benefits of radiation therapy as adjuvant treatment in patients with low-risk carcinoma of the mammary gland: taking cutaneous postradiation angiosarcoma as an opportunity for a critical appraisal of postoperative radiotherapy. *Ann Oncol* 2007;**18**:619–21.