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Clinical management of secondary angiosarcoma after breast conservation therapy

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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.

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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.