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Original article

# Angiosarcoma associated with radiation therapy after treatment of breast cancer. Retrospective study on ten years

## *Angiosarcomes associés à la radiothérapie après un traitement pour cancer du sein. Étude rétrospective sur dix ans*

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ABSTRACT

*Purpose.* – The breast sarcoma induced by radiation therapy is rare but increasing, given the increased long-term survival of patients receiving radiation therapy. Fibrosarcoma, histiocytofibroma and angiosarcoma are the most common breast sarcoma. Angiosarcoma is the most common after breast cancer treated by radiation therapy, often diagnosed too late, with a severe prognosis and a high rate of recurrence. However, because of the low incidence of angiosarcoma associated with radiation therapy (AAR), the benefit of radiation therapy in breast cancer treatment outweighs the risk to develop angiosarcoma. The aim of this study is to evaluate these rare cases of AAR diagnosed in eastern Belgium in comparison to the data from the literature.
*Patients and methods.* – Nine cases of AAR after radiation for breast ductal carcinoma were included in this retrospective study. AAR was diagnosed according to Cahan criteria between January 2007 and December 2016. Latency, incidence, management and prognosis are comparable to the literature.
*Results, conclusion.* – The median latency was 10 (4–24) years, the incidence of AAR in the East Belgian area was 0.09% of the patients irradiated on the same period. Patients were treated by surgery with wide local excision with or without reconstructive surgery, without radiotherapy and chemotherapy treatment. Kaplan-Meier analysis showed median overall survival of 61.8 months, patient survival of 55.6% at one year and 29.6% at five years. With the constant progress of medicine and its technologies, it would be possible to limit the occurrence of AAR or to diagnose it at an earlier stage.


*Mots clés :*
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RÉSUMÉ

*Objectif de l'étude.* – L'incidence du sarcome du sein diagnostiqué après une radiothérapie est rare, mais en augmentation compte tenu de l'augmentation de l'espérance de vie des patients après radiothérapie. Le fibrosarcome, l'histiocytofibrome et l'angiosarcome sont les sarcomes du sein les plus courants. L'angiosarcome est fréquemment diagnostiqué chez les patients ayant bénéficiés d'une radiothérapie pour cancer du sein. Diagnostiqué trop tard, l'angiosarcome a un pronostic défavorable, un taux élevé de

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récidive. Cependant, vu son faible incidence, le bénéfice d'une irradiation dans le cadre d'un cancer du sein dépasse ce risque. L'objectif de ce travail était d'évaluer les cas d'angiosarcomes après une radiothérapie et de comparer ces données à la littérature.
*Patients et méthodes.* – Cette étude rétrospective a inclus neuf patientes atteintes entre janvier 2007 et décembre 2016 d'un angiosarcome après radiothérapie d'un carcinome canalaire du sein. La latence, l'incidence, la prise en charge et l'évolution des patientes ont été comparées à la littérature.
*Résultats, conclusion.* – La latence médiane était de 10 (4–24) ans, l'incidence était de 0,09 % des patients irradiés sur la même période dans l'Est de la Belgique. Les patientes ont été traitées par chirurgie avec ou sans reconstruction, sans radio- ni chimiothérapie. La survie globale était de 61,8 mois, avec une probabilité à un an de 55,6 % et à cinq ans de 29,6 %. Les progrès constants de la médecine et de ses technologies permettront de limiter la survenue de ce type d'angiosarcome et/ou de les diagnostiquer plus précocement.


## 1. Introduction

The term "radiation-induced sarcoma" is used inappropriately. It is preferable to use the term "sarcoma associated with radiation therapy" because radiation-induced sarcoma implies that radiation therapy is the only etiological factor, omitting other potential features that may contribute to their occurrence [1]. Sarcoma associated with radiotherapy is a secondary cancer developing after irradiation and corresponds to 3 to 6% of all sarcomas [2]. These cancers develop in the irradiated volume or in the twilight zone, at the limit of the irradiation field, where the radiation is not homogeneous [3,4]. It may be insufficient to cause apoptosis of tumor cells but sufficient to cause genetic mutations in surviving cells. Due to long-term survival of patients treated with radiotherapy for breast cancer, the incidence of sarcoma associated with radiotherapy is increasing though remaining rare. Angiosarcoma, sarcoma originates from vascular endothelial cells, is the most common histological type encountered after breast conservative surgery and irradiation, with incidence estimated between 0.04 and 0.15% [1]. The absolute risk of angiosarcoma associated with radiotherapy (AAR) is evaluated at seven per 100,000 person-years after conservative treatment of breast cancer in the USA [5]. The clinical presentation of AAR is cutaneous with thickening, erythema, nodule, and discoloration of the skin that can be confused with benign lesions (sequelae of radiotherapy, cellulitis, hematoma) [6].

Carcinogenesis is multifactorial, possibly mixed with intrinsic and extrinsic factors. The first is the young age during treatment and genetic predisposition (Li-Fraumeni syndrome, familial adenomatous polyposis, etc); the second is the use of radiotherapy (iatrogenic), as well as the combination with chemotherapy [7]. The long-term survival of breast cancer is improved by early diagnosis following screening campaigns, fast and effective management. Therefore, this influences the occurrence of a sarcoma after radiotherapy for breast carcinoma, which is diagnosed from six months to 44 years after the initiation of radiotherapy with an average latency of 10 years [6]. This average latency can be shorter (four to eight years) for angiosarcoma [2]. Beside radiotherapy, chronic arm or breast edema is also considered as risk factor of AAR [6].

The four criteria of Cahan allows to differentiate a sarcoma associated with radiotherapy than a sporadic sarcoma [8]: prior irradiation, localization of sarcoma in the irradiated volume, latency period of minimum five years, histology of the first tumor different from the sarcoma associated with radiation. Confirmation of histological diagnosis is performed by biopsy. However, the anatomopathological analysis does not differentiate a primary sarcoma from a secondary one. Cahan's criteria and genomic studies are underway to remedy this. At the moment, evidence of significant amplification of the MYC gene on locus 8q24.21 (an oncogene acting on growth and death accelerating carcinogenesis) was found in 100 to 50% of sarcoma associated with radiotherapy [2,9,10].

Given the rarity of the pathology, there is no real treatment recommendation in the literature. The extensive radical surgery, associated or not with reconstructive surgery, is the only effective treatment. This is a challenging curative approach because AAR is often an extensive and multi focal disease [11]. Radiotherapy and chemotherapy still have an uncertain place. The prognosis of the sarcoma associated with radiotherapy is unfavorable with five-year survival rate varies between 10 and 50% depending on the studies [2]. AAR is aggressive tumour, high grade by definition. Diagnosis is often late. After surgical resections, the margins are frequently positive on histology. All of these factors explain a high rate of local recurrence and metastasis [2].

The purpose of this retrospective study is to know more concretely what we are talking about, to quantify and to evaluate these rare cases within the east Belgian area in comparison to the data from the literature: incidence, time to onset, treatment, histology and prognosis of these rare tumours.

## 2. Patients and methods

This retrospective study included patients who developed an AAR after radiation for breast ductal carcinoma according to revised Cahan criteria [8]. Patients with a suspected lesion of AAR but not histologically confirmed were excluded. Patients were irradiated in the radiotherapy departments of the University of Liege or in the radiotherapy departments of the Verviers Regional Hospital Center. All AAR was confirmed by anatomopathological analysis specifically in the department of anatomopathology of the « CHC Groupe Santé » between January 2007 and December 2016. Under these criteria, nine cases were identified: one irradiated in 1987 at the University of Liege and eight irradiated between 1998 and 2011 (7 in Liege and 1 in Verviers).

Patient's data regarding age, type of surgery for the breast cancer, latency, history of irradiation and information on the AAR were obtained from hospital care records. The preoperative assessment (including PET scan, MRI and/or bone scintigraphy) allowed to exclude a metastatic disease. The medical record of all patients ($n = 9$) was discussed during a multidisciplinary meeting of oncology in order to validate the treatment plan. The latency was defined as the time period in years between the date of completion of radiotherapy for breast cancer and the histological diagnosis of the AAR.

All analysis were performed using the R software (version 3.4.0) with the « survival » package [12]. Follow-up time was presented as median with range (min–max). Overall survival was defined as time from AAR diagnosis to death or last follow-up. All cause of death were discussed, and confirmed to be associated to AAR.

**Table 1**
Summary of clinico-pathologic data of breast carcinoma and angiosarcoma in the study population.

| Patient | Breast carcinoma | | | | | Angiosarcoma | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Age at diagnostic (years) | Tumor stage | Histology | Treatment before radiotherapy | Radiotherapy, source dose | Age at diagnostic (years) | Latency (years) | Size (mm) | Follow-up (months) |
| 1 | 56 | T1NxM0 | Invasive ductal carcinoma | Mastectomy + lymph node dissection + chemotherapy | NA, no boost (mastectomy) | 81 | 24 | 23 | 22 (dead) |
| 2 | 69 | T1NxM0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons + electrons, 50 + 10 Gy | 82 | 12 | 15 | 10 (dead) |
| 3 | 49 | T1N0M0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons, 46 Gy | 64 | 14 | NA | 80 |
| 4 | 47 | T1N0M0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection + chemotherapy | Photons, 46 Gy | 58 | 10 | 20 | 54 (dead) |
| 5 | 66 | T1NxM0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons, 46 Gy (internal mammary nodes) | 73 | 6 | 110 | 110 (dead) |
| 6 | 77 | NA | NA | NA | Photons + HDR, 46 + 6 Gy | 93 | 15 | 90 | 1 (dead) |
| 7 | 74 | T1N0M0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons, 50 Gy | 82 | 7 | 80 | 7 (dead) |
| 8 | 78 | T2N0M0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons + electrons, 42 + 10 Gy | 83 | 4 | 70 | 3 (dead) |
| 9 | 61 | T1N0M0 | Invasive ductal carcinoma | Tumorectomy + lymph node dissection | Photons + HDR, 43 + 7.7 Gy | 67 | 5 | 20 | 44 |

NA: not available.

Survival analyses were conducted in compliance with Definitions for the Assessment of Time-to-Event Endpoints in Cancer Trials (DATECAN) recommendations. Survival curve was computed using the Kaplan-Meier method. Due to a small sample of nine patients, we did not study the difference in survival among subsets (tumor differentiation or tumor size) with the log rank test and cox proportional hazards model, multivariate analysis. We compared the number of events five years after AAR diagnosis in groups of tumor differentiation (well versus poorly or moderately) and in groups of tumor size (> versus < 50 mm) by the Fisher exact test. A $P$ value < 0.10 was set as our threshold for statistical significance.

## 3. Results

We identified nine women with histologically verified AAR, after surgery and postoperative radiotherapy for invasive or *in situ* breast ductal carcinoma, cured of their breast cancer. Characteristics and treatments are described in Table 1. The median age at diagnosis of breast carcinoma was 66 (47–78) years old. Note that patient number 1 diagnosed with AAR on the right breast side in 2011 developed three previous cancers: in 1971 breast cancer on the left side (invasive epithelioma low differentiated) treated with surgery and adjuvant radiotherapy, in 1987 breast cancer on the right side treated with surgery and adjuvant radiotherapy and chemotherapy (three cycles of 5-fluorouracil epirubicin cyclophosphamide) and finally in 1999 esophagus neoplasia treated with endoscopy, chemotherapy and radiotherapy. Unfortunately, there were missing data about the radiotherapy administrated in 1987 for the breast cancer on the right side. None of the patients in our study received neo adjuvant treatment for breast cancer. Patient number 6 had missing data about treatment before radiotherapy for breast cancer. All patient received radiation on the breast or the chest wall excepted patient number 5 whose received complementary radiotherapy on the internal mammary node (30 Gy).

Patient demographics and AAR characteristics are summarized in Table 1. The median age at diagnosis of AAR was 81 (58-93) years old, with a median latency of 10 (4-24) years. Of the nine patients included in our study, eight patients had a localized AAR on the previous irradiated breast area treated by radical surgery. One patient (patient number 1) had a AAR below the clavicle treated by local excision. Multidisciplinary meeting of oncology decided that none was treated with radiotherapy or chemotherapy before surgery. Patient 1 had an excision lesion of the thoracic wall below the clavicule area, without reconstructive surgery. Patients 2, 6, 7 and 8 had mastectomy without immediate reconstructive surgery because they are elderly patient (> 82 years old at AAR diagnosis) not asking for a reconstruction surgery. In contrary, younger patients 3, 4 and 9 (58 to 67 years old) were asking for a immediate breast reconstruction with deep inferior epigastric perforator (DIEP) after mastectomy. Because of internal localization of the lesion, patient number 5 had bilateral mastectomy with removal of the associated anterior chest wall and reconstructive surgery with abdominal advancement flap to allow skin closure.

Two patients had palliative mastectomy with tumor margins microscopically positive (R1 resection), patient number 7 who died 7 months after AAR surgery and patient number 8 who died 3 months after surgery. Of the seven patients with a microscopically negative R0 resection, three patients had local recurrence developed after a median of 26 (5-63) months after surgery. The median survival without recurrence in our sample is 22 (1-79) months. Recurrences were treated by palliative chemotherapy or curative surgery. After total excision surgery, patient number 4 developed unfortunately local recurrence three times until death.

No adjuvant radiotherapy or chemotherapy was administered after surgery for AAR because patients were considered too old or in poor condition. Only patient number 6 received hormonotherapy for a controlateral breast invasive ductal carcinoma.

Within 30 days after surgery, no patients died and there were morbidity for three patients: recurrent lymphocele, cutaneous necrosis, abscess at the abdominal site requiring reoperation. Of the nine patients, five patients died of causes associated to the AAR and two of other cause. Death occurs on average 30 months after the AAR diagnosis. Two patients still alive with a follow-up of 44 and 80 months. The median overall survival was 61.8 months, one- and five-year survival after AAR diagnosis were respectively 55.6% ± 16.6% and 29.6% ± 16.4% (Table 2). The number of deaths five years after the AAR diagnosis in groups of tumor size (> 50 mm versus < 50 mm; $P$ > 0.99) was not statistically different. The poorly or moderately differentiated tumor group underwent significantly more deaths five years after surgery than the well differentiated tumor group, $P$ > 0.083.

**Table 2**
Survival table.

| Time (months) | Survival (%) | Confidence interval 95% | Number of patient at risk |
|---|---|---|---|
| 1.4 | 88.9 | 43.3;98.4 | 9 |
| 3.5 | 77.8 | 36.5;93.9 | 8 |
| 8.0 | 66.7 | 28.2;87.8 | 7 |
| 10.2 | 55.6 | 20.4;80.5 | 6 |
| 12.0 | 55.6 | 20.4;80.5 | 6 |
| 22.2 | 44.4 | 13.6;71.9 | 5 |
| 36.0 | 44.4 | 13.6;71.9 | 5 |
| 43.7[a] | | | 4 |
| 55.0 | 29.6 | 5.2;60.7 | 3 |
| 60.0 | 29.6 | 5.2;60.7 | 3 |
| 79.[a]* | | | 2 |
| 110.4 | 0 | | 1 |

[a] Patients still alive.

## 4. Discussion

Given the rarity of the pathology and the insidious clinical presentation mistaken for cellulitis or a hematoma, the diagnosis can be delayed, worsening the poor prognosis, or the disease cannot be diagnosed which makes the assessment of the incidence difficult to appreciate [2].

In our study, the delayed diagnosis was mainly due to late consultation of the elderly patient or diagnosis error. We diagnosed 9 patients with AAR between January 2007 and December 2016 after breast cancer treated by surgery and radiotherapy. Among this sample, one patient benefited from radiotherapy in 1987 at the University of Liege while the other eight between 1998 and 2011 in the two radiotherapy departments of the East Belgian area (University of Liege and Verviers Regional Hospital Center). On this period 1998 and 2011, a total of 9 368 patients were treated after surgery for breast cancer in this two radiotherapy departments. For the reasons given above, the real risk was difficult to appreciate, definitely undervalued. We estimated that the incidence of AAR after treatment of breast cancer incidence in the East Belgian area is 0.09% of the patients irradiated on the same period. The same incidence was estimated in larger series in France and USA [13,14]. According to the Belgian Cancer Registry, the incidence of angiosarcoma of the breast was 0.12 per 100.000 inhabitants (crude rate, both genders, Belgium, 2007–2016). However, it was not possible to determine which ones are associated with irradiated breast cancer.

Angiosarcoma was the only histological type included in our study and the histological type most frequently found after breast irradiation [2]. In the literature, the use of chemotherapy after breast cancer increased the risk of AAR [15], which was not the case in our series where only two patients received adjuvant chemotherapy for breast cancer. Our retrospective study on this rare cancer did not permit us to find other associated factor that could explain the occurrence of AAR. Despite evidence of significant amplification of the MYC gene in some sarcoma associated with radiotherapy, this genetic alteration has not been studied in our sample [2,9,10]. Created in 2011, the SARI study, which included 120 patients with a sarcoma associated with radiotherapy compared to 240 controls, was designed to determine the clinical and biological risk factors predictive of sarcoma associated with radiotherapy. Results of this study revealed RILA biomarker, an interesting indicator [16].

The latency of AAR was relatively short compared to other histological types [2]. It should be pointed out that in our study the extreme delay in onset of AAR was 24 years because the patient number 1 was irradiated in 1987 for breast cancer and in 1999 for esophagus cancer. The occurrence of AAR in 2011 may be related to the second treatment, the cumulation of both, especially since the location of the AAR was below the clavicle area. This patient may be a bias in the analysis. If this clinical case is omitted, the median latency is 9 years instead of 10 years, latency periods comparable to other reports [1,13,14].

Despite the fact that surgery was a challenging curative approach due to this multi focal disease, surgery was the only treatment approved and recognized in the literature [17]. In our study, eight patients underwent radical mastectomy and one cleanliness surgery. Surgery on irradiated site could be delicate because it was difficult to evaluate the slices of sections and healthy margin. Due this decaying surgery, it was also difficult to close the plans [18]. Reconstructive surgery is essential, if possible. However, it is recommended to delay reconstructive surgery given the high risk of local recurrence (according to some studies up to 73%) and to use a technique of temporary coverage until confirmation of healthy surgical section slices in histology. The reconstruction techniques used are skin grafts, abdominal advancement flap, musculocutaneous flaps, deep inferior epigastric perforator (DIEP) allowing a correction of the covering defect and the volume. Given the high rate of local recurrence, reconstruction is to be considered in a second step [17]. In our study, three patients underwent mastectomy associated with immediate breast reconstruction thanks to small size of the tumour. Among these three patients, one developed recurrence and died, two still alive with complete remission three and six years after surgery. No adjuvant treatment was given while chemotherapy would appear to decrease the local recurrence rate [1]. Depla et al. proposed radiotherapy adjuvant for local control [19]. The role of radiotherapy and chemotherapy remains uncertain [2]. Neoadjuvant treatments are proposed with promising results to allow to surgical resection [20–22]. AAR, usually very aggressive locally, gives premature metastases, most often in the lung and liver, less in the bones, brain, skin and contralateral breast [6,17]. In this case of metastatic diseases, paclitaxel and angiogenesis inhibitors have shown some efficacy in AAR treatment [1,17,23]. In our study, all recurrences were locoregional. Torres et al. [1] realized an average follow-up of 11 years of a sample of 95 cases of AAR (after treatment of breast cancer) and observed a local recurrence in 48% of patients with 27% with metastases. The prognosis of AAR remains dark with a five-year survival of 30% in our little sample and between 20 and 54% in the literature [1,24,25].

In conclusion, AAR is an insidious cancer under-reported, with a delayed diagnosis, darkness prognosis despite surgery with sufficient margins. The therapeutic possibilities remain reduced. With a very long-term postradiotherapy monitoring with biopsy of suspicious breast skin lesion, with identification of subjects at risk with genetic signatures and with new radiation techniques, it is possible to diagnose early and to treat quickly these malignant lesions of the vascular endothelium. Intensity-modulated radiation (IMRT) may help, not verified in the literature [2]. Studies on targeted immunotherapy are in progress [26]. With larger patient studies and more reflexions on the subject, it will be possible to prevent and treat adequately this highly aggressive and malignant disease originating from endothelial cells.

## Disclosure of interest

The authors declare that they have no competing interest.

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