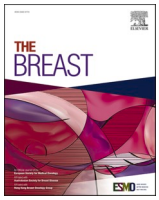
The Breast 78 (2024) 103825

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast



# Neoadjuvant chemotherapy for radiation associated angiosarcoma (RAAS) of the breast: A retrospective single center study

Stijn J.C. van der Burg [a], Sophie J.M. Reijers [a], Anke Kuijpers [a], Lotte Heimans [b], Astrid N. Scholten [c], Rick L.M. Haas [c], Hester van Boven [d], Willemijn M. Kolff [e], Marie-Jeanne T.F.D. Vrancken Peeters [a], Martijn Kerst [b], Beatrijs A. Seinstra [f], Neeltje Steeghs [b], Winette T.A. van der Graaf [b], Yvonne M. Schrage [a], Winan J. van Houdt [a,*]

[a] Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Department of Surgical Oncology, Plesmanlaan 121, Amsterdam, the Netherlands
[b] Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Department of Medical Oncology, Plesmanlaan 121, Amsterdam, the Netherlands
[c] Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Department of Radiotherapy, Plesmanlaan 121, Amsterdam, the Netherlands
[d] Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Department of Pathology, Plesmanlaan 121, Amsterdam, the Netherlands
[e] Amsterdam University Medical Centre, Department of Radiotherapy, Meibergdreef 9, Amsterdam, the Netherlands
[f] Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI-AVL), Department of Radiology, Plesmanlaan 121, Amsterdam, the Netherlands

A B S T R A C T

*Background:* Radiation associated angiosarcoma (RAAS) of the breast is a rare malignancy with poor survival. Optimal treatment strategies remain uncertain due to a lack of data, and vary between surgery alone and a combination of surgery with (neo)adjuvant chemotherapy (NACT) and/or re-irradiation. The aim of this study was to evaluate the potential benefit of taxane based NACT.

*Methods:* In this retrospective single center study, all patients with RAAS of the breast treated between 1994 and 2024 are included. Since 2018, NACT is considered a treatment option for this patient population in our institute. The difference in oncological outcomes of patients with and without NACT were compared.

*Results:* Thirty-five women were included. Thirteen (37 %) received NACT of which five (39 %) also had neoadjuvant re-irradiation with hyperthermia. Eleven patients (85 %) received paclitaxel, the other two (15 %) had doxorubicine/docetaxel. Complete pathological response was found in 69 % (n = 9). Median follow up was 41 months (range 24–56) for patients with NACT and 44 (range 20–108) for patients without NACT. In the NACT group, only one patient developed a recurrence after 6.5 years. Patients with NACT had improved oncological outcomes compared to patients without NACT in terms of 3-year local recurrence free survival (100% vs. 63.9 %, p = 0.14), distant metastasis free survival (100 % vs. 47.5 %, p = 0.005), and overall survival (100% vs. 56.1 %, p = 0.016).

*Conclusion:* In this study, neoadjuvant taxanes for RAAS of the breast leads to improved distant metastasis free survival and overal survival in patients treated with NACT compared to no NACT

## 1. Introduction

Angiosarcoma is a rare and aggressive malignancy, which originates from vascular endothelial cells and comprises 2–4% of all soft tissue sarcomas. Half of the angiosarcomas arise from the skin, and the breast is the most common location [1,2]. Although the etiology of angiosarcoma is poorly understood, a differentiation is made between primary and secondary angiosarcomas [3]. Secondary angiosarcomas can be sub-classified as ultraviolet associated, chronic lymphedema associated (Stewart-Treves), or radiotherapy associated [1,4].

Most radiation associated angiosarcomas (RAAS) are localized in the breast due to the high incidence of breast cancer and the high proportion of those patients being treated with adjuvant radiotherapy. The risk of developing RAAS after radiotherapy for breast cancer is 0.1 % in the Dutch population, while other studies mention 0.14 % and 0.5 % [5–7]. While RAAS comprises only 0.04–0.05 of all breast malignancies, it is the most prevalent post radiation sarcoma for this location [3,8]. Due to the rarity of the disease, it is often not recognized or diagnosed late and therefore underreported. Still, the incidence is rising, most likely since the survival of breast cancer patients who had radiotherapy is increasing [9]. The 5-year overall survival (OS) from RAAS of the breast varies from 28 % to 54 % [2,3,8].

RAAS often starts as a yellow, blue, or red patch in the previously irradiated skin and is often confused with a hematoma [8]. Pathologic evaluation after biopsy is the most sensitive method to diagnose RAAS and especially the presence of *C-MYC* amplification helps to distinguish

* Corresponding author. Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital (NKI-AVL), Plesmanlaan 121, 1066 CX, Amsterdam the Netherlands.
*E-mail address:* w.v.houdt@nki.nl (W.J. van Houdt).

https://doi.org/10.1016/j.breast.2024.103825
Received 27 August 2024; Received in revised form 17 October 2024; Accepted 20 October 2024
Available online 21 October 2024

RAAS from other atypical vascular lesions [10,11]. Diagnosis is usually made clinically, which can be assisted by mammography and ultrasound, although these modalities are often unreliable [11]. Magnetic resonance imaging (MRI) can be used to further evaluate the extent of the tumor at diagnosis and to monitor treatment effect in the neoadjuvant setting. 18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography computed tomography (PET-CT) is most helpful in detecting metastases [12].

There is no consensus on the optimal treatment for RAAS of the breast [3,8,13]. The mainstay of treatment is a wide excision, usually a mastectomy including all of the irradiated skin, with negative resection margins [14]. Currently, there is no solid evidence on the use of (neo) adjuvant systemic treatment or re-irradiation combined with hyperthermia. However, (neo)adjuvant re-irradiation combined with hyperthermia has shown some promising results in previous reports [15–18]. Systemic treatment in the primary setting has been described, but the indication and the treatment of choice is a topic for debate, although some good results have been seen with taxanes [3,8,13].

Since 2018, neoadjuvant chemotherapy, preferably paclitaxel, is considered standard of care for patients with a first presentation of RAAS of the breast in our institute. The aim of this study was to evaluate the difference in local recurrence free survival (LRFS), distant metastasis free survival (DMFS) and OS between patients treated with or without neo-adjuvant taxanes before local treatment.

## 2. Methods

All consecutive patients with a first presentation of RAAS of the breast and treated at our institution between 1994 and 2024 were retrospectively selected and included in this study. The diagnosis of all cases was confirmed by an expert pathologist. Prior to 2018, the standard treatment approach consisted of complete resection of the RAAS, including all irradiated skin and soft tissue. In case of positive resection margins, a re-resection or adjuvant re-irradiation with hyperthermia was considered. Since 2018, NACT was considered for all patients for RAAS of the breast, with the addition of neoadjuvant re-irradiation combined with hyperthermia for extensive disease. All treatment plans were discussed in multidisciplinary tumor board (MTB) meetings, with at least a surgeon, oncologist, radiologist, pathologist, radiation oncologist, and a plastic surgeon since 2010.

With approval of the local ethical committee (IRBd24-107, 04-04-2024) patient characteristics, treatment characteristics, and oncologic outcomes were collected from electronic patient files. Included variables were age at diagnosis, size, sex, radiotherapy (RT) - RAAS interval, type of chemotherapy, number of cycles of chemotherapy, use of radiotherapy, clinical, radiological, metabolic and pathological response, whether a re-resection was necessary, and if plastic reconstruction was performed. The primary endpoints were LRFS, DMFS and OS. LRFS was defined as the period between final resection and a local recurrence. DMFS and OS were defined as the period between treatment and distant metastasis or death, respectively. The secondary endpoint was pathological response to NACT.

### 2.1. Statistical analysis

Descriptive analyses utilized standard statistical measures such as medians with interquartile ranges (IQR) and means with standard deviations. Independent T-tests, Mann–Whitney U tests or Pearson's chi-square tests were used to compare means, medians and ordinal data, respectively. Cumulative incidence curves with Grey's test were used to analyze LRFS and DMFS and a Kaplan-Meijer curve with the log rank test was used for OS. Analyses were conducted using IBM SPSS 27.0 for Windows and RStudio version 4.2.

## 3. Results

Between October 1994 and September 2023, 35 patients with primary RAAS of the breast were surgically treated in our institution. All patients were female and the mean age was 64. Thirteen (37 %) patients received NACT, while 22 (63 %) did not. The first patient receiving NACT was treated in 2017. Since 2018, all patients with primary RAAS of the breast received NACT, except for one patient who refused. In the group without NACT, four patients had an R1 resection while all patients with NACT had an R0 resection ($p = 0.116$). Three patients with an R1 resection had a re-excision (all R0) and one patient received adjuvant re-irradiation. All patient and treatment characteristics are displayed in Table 1.

The group with NACT received significantly more RT combined with hyperthermia ($p = 0.025$). Four patients (18 %) had re-irradiation with hyperthermia in the group without NACT, of which 1 in the neoadjuvant setting (25 %), versus 7 (46 %) in the NACT group, of which 5 in the neoadjuvant setting (71.4 %). The dose was either 8 times 4 Gy in 4 weeks with once weekly hyperthermia or 23 times 2 Gy in 4.5 weeks with once weekly hyperthermia. Two of the six (33.3 %) patients with neoadjuvant re-irradiation with hyperthermia had a wound infection.

The majority (84.6 %) of the patients received 80mg/m2 paclitaxel on day 1, 8, and 15 in a 4 week cycle. One patient (7.7 %) who received paclitaxel had a 25 % dose reduction for the fourth and last cycle due to complaints of neuropathy Common Terminology Criteria for Adverse Events (CTCAE) grade 2 and fatigue CTCAE grade 2. Four or six cycles of NACT were given in all patients except in one patient who received 8 cycles of paclitaxel as a combination treatment with Trastuzumab because of a concurrent primary breast cancer in the other breast. Of the eight patients with NACT without neoadjuvant re-irradiation, one (17 %) had a wound infection. All NACT characteristics are displayed in Table 2.

In the NACT group, twelve (92 %) patients showed a clinical response, of the 12 patients with MRI before and after NACT, three (25 %) and five (42 %) had complete or partial response (PR), respectively. Four patients (33 %) had a PET/CT before and after NACT, and two of them had a metabolic complete response and two a partial metabolic

**Table 1**
Patient and treatment characteristics per group treated without neoadjuvant chemotherapy (NACT) and with NACT

| | Without NACT | | With NACT | | p value |
|---|---|---|---|---|---|
| | n= 22 | (%) | n= 13 | (%) | |
| Diagnosis AS between: | | | | | |
| 1994-2003 | 6 | (27) | 0 | | **<0.001** |
| 2004-2013 | 11 | (50) | 0 | | |
| 2014-2023 | 5 | (23) | 13 | (100) | |
| Age (SD) | 65 | (11) | 64 | (10) | 0.770 |
| Woman | 22 | (100) | 13 | (100) | |
| Interval MC/RAAS (years)(IQR) | 7 | (5-10) | 7 | (5-10) | 0.973 |
| Size | | | | | |
| ≤5 cm | 9 | (41) | 6 | (46) | 0.713 |
| >5 cm | 8 | (37) | 7 | (54) | |
| Missing | 5 | (22) | 0 | | |
| Radiotherapy/Hyperthermia | | | | | |
| Yes | 4 | (18) | 7 | (54) | **0.028** |
| No | 18 | (82) | 6 | (46) | |
| Margins | | | | | |
| R0 | 18 | (81) | 13 | (100) | 0.102 |
| R1 | 4 | (19) | 0 | | |
| Re-excision | | | | | |
| Yes | 3 | (14) | 0 | | 0.164 |
| No | 19 | (86) | 13 | (100) | |
| Plastic reconstruction | | | | | |
| Yes | 15 | (68) | 12 | (92) | 0.101 |
| No | 7 | (32) | 1 | (8) | |

Values are n (%) unless otherwise indicated. Abbreviations: NACT = neoadjuvant chemotherapy, MC= mammacarcinoom, RAAS = radiotherapy associated angiosarcoma.

**Table 2**
Neoadjuvant chemotherapy characteristics

| | NACT group (n=13 (%)) | |
|---|---|---|
| Type of chemotherapy | | |
| Paclitaxel (80mg/m2) | 11 | (85) |
| Doxorubicine (60mg/m2)/docetaxel (75mg/m2) Cycles | 2 | (15) |
| 4 | 6 | (46) |
| 6 | 6 | (46) |
| 8 | 1 | (8) |
| Dose reduction due to toxicity | | |
| Yes | 1 | (8) |
| No | 12 | (92) |

Values are n (%). Abbreviations: NACT = neoadjuvant chemotherapy

response (Figs. 1A,2). Pathological evaluation after surgery showed a complete response (pCR) in nine patients (69 %). Two patients without pathological complete response had 1 % vital cells, the third had 5 %, and the fourth had 70 % vital cells (Fig. 1B).

The median follow up was 41 months (range 21–84) since start of the first treatment for all patients, with 41 months (range 24–56) for patients with NACT, and 44 months (range 20–108) for patients without NAC. Before 2016, the follow up occurred every 6 months and after 2016 the frequency increased to every 4 months. No metastasis or death occurred in the NACT group, but one patient (7.7 %) developed a local recurrence after 6.5 years. Of the patients without NACT, 9 patients (41 %) had a local recurrence, 11 had distant metastases (50 %), and 12 died (55 %). One death was not disease related. Seven out of 9 (78 %) patients recurred locally in the first three years, while 11 out of 11 (100 %) patients metastasized within this period. Patients with NACT had improved oncological outcomes compared to patients without NACT in terms of 3-year LRFS (100 % vs. 63.9 %; p = 0.140), 3-year DMFS (100 % vs. 47.5 %, p = 0.005)(Fig. 3), and 3-year OS (100 % vs. 56.1 %; p = 0.016) (Fig. 4).

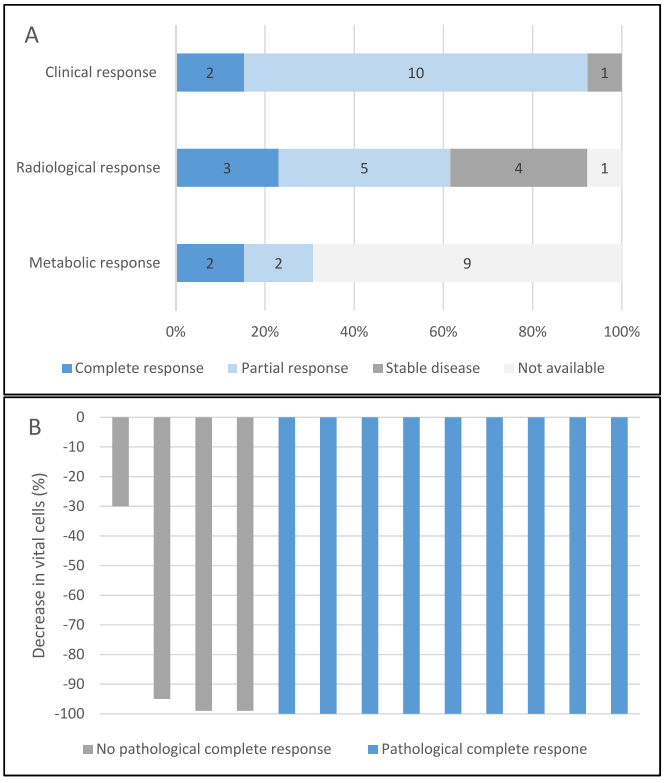



**Fig. 1.** (A) Different outcomes of clinical, radiological (MRI), and metabolic response evaluation after neoadjuvant chemotherapy (NACT). Partial response is defined as every state between complete response and stable disease. Stable disease is defined as no change before and after NACT. (B) A waterfall plot demonstrating the response per patient in terms of decrease in vital cells. (single column fitting image, in color).

## 4. Discussion

In this retrospective single center cohort study, the effect of NACT for RAAS of the breast on oncological outcomes was evaluated. No metastases or deaths were observed in the group receiving NACT years with a median follow up of 41 months and only one recurrence after 6.5 years occurred. Due to the rarity of the disease, a limited number of patients was included which prohibited extensive statistical analyses. Still, a trend towards improved oncological outcomes was observed for patients who received NACT, which was statistically significant for DMFS and OS. The high percentages of pathological response further support the positive trend in results following NACT for these patients. While caution is necessary with interpreting these findings because of the small cohort, the observed improvements in oncological outcomes for this rare disease warrant confirmation in larger prospective studies.

The overall survival in the group without NACT was in line with the described 5-year overall survival rate for RAAS of the breast of 28 %–54 % [2,3,8], since almost all events occurred in the first 3 years. The outcomes we describe after NACT are in line with other reports by the Mayo Clinic and the Cleveland Clinic [17,18]. The study from Mayo Clinic compared 16 patients who had neoadjuvant trimodality treatment (paclitaxel, radiotherapy and surgery) with 22 patients with mono/dual therapy. A median of 3 cycles (range: 2–4 cycles) 80 mg/m2 paclitaxel was given followed by concurrent paclitaxel with re-irradiation (median dose 50.0 Gy). Five year LRFS, DMFS and OS in the trimodality group were 100 %, 93.8 %, and 100 %, respectively, and a pCR of 75 % was observed. The Cleveland Clinic treated eight patients with neoadjuvant re-irradiation (60–69 Gy) of which 7 received neoadjuvant taxanes as well. Dose and number of cycles were not specified. The median follow-up was 34 months (range, 23–76 months) and at last follow up 88 % of the patients was disease free. Pathological complete response was observed in 62.5 %. Although these studies are somewhat similar to our study, the focus of the studies do vary. The Mayo clinic study focused on the effect of trimodality treatment, the Cleveland Clinic study focused on the role of re-irradiation, while our study aimed to evaluate the role of neo-adjuvant taxanes.

Other studies describing NACT for angiosarcoma mention a general beneficial effect, but no clear improvement in oncological outcomes were shown [19–24]. Comparison with our cohort is complicated due to the heterogeneity and methodology of these other studies. Multiple types and multiple anatomical sites of angiosarcoma were included in those studies and the use of 16 different chemotherapy types were described. For re-irradiation, more series specifically about RAAS of the breast are published. A systematic review and a meta-analysis both conclude that re-irradiation for this patient population improves LRFS [25,26]. In a study including 14 patients, who gave hyperfractionated accelerated re-irradiation followed by surgery, a ten-year disease specific survival of 71 % was seen [27]. Re-irradiation in the neoadjuvant setting mainly improved the rate of negative resection margins [28].

Based on our data and the existing literature described above, NACT seems to improve oncological outcomes for specifically RAAS of the breast. Poorer improvements were seen in more heterogeneous groups of angiosarcoma, suggesting that NACT with taxanes works best for this subtype of angiosarcoma. Whether re-irradiation with hyperthermia still needs to be given after a (near) pathological complete response after NACT is open for debate. The Mayo Clinic and the Cleveland Clinic treated almost all of their patients with NACT and neoadjuvant re-irradiation without hyperthermia. Meanwhile, the oncological outcomes and pathological response were similar to our study.

Based on these findings, even with the small numbers of included patients, one might hypothesize that NACT alone has the same effect as a combination of NACT and re-irradiation without hyperthermia. An

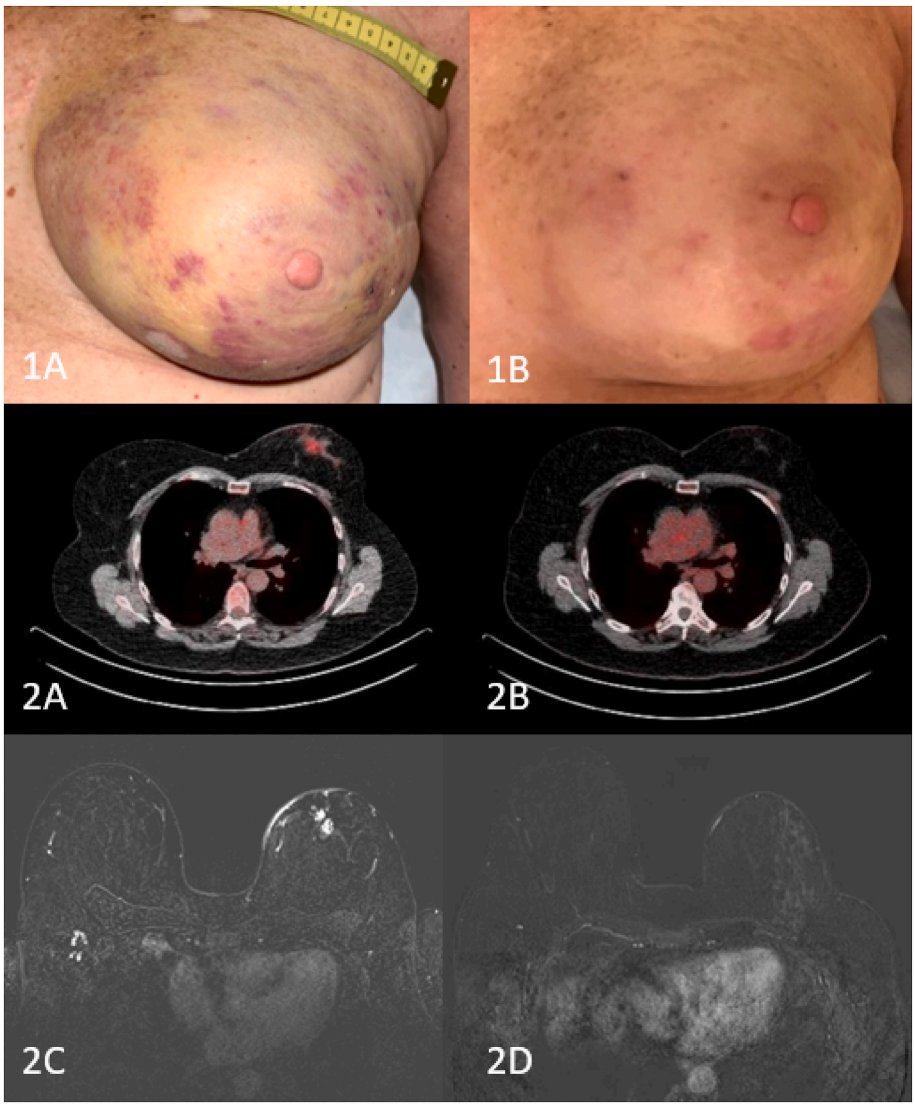



**Fig. 2.** [1] A radiation associated angiosarcoma (RAAS) of the breast before (A) and after (B) four cycles of paclitaxel [2]. A fludeoxyglucose-18 positron emission tomography/computed tomography and magnetic resonance imaging of a patient with RAAS of the breast before (A,C) and after (B,D) six cycles of paclitaxel. (Images used with approval of patients) (single column fitting image, in color).

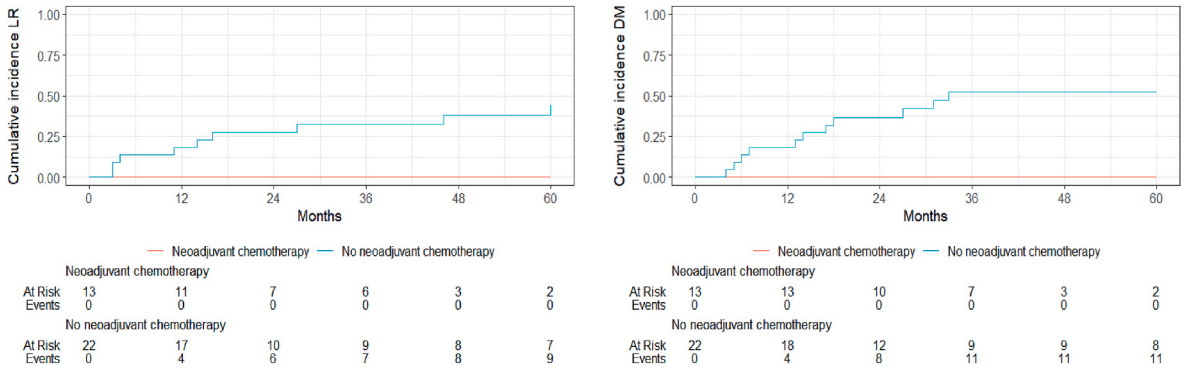



**Fig. 3.** Cumulative incidence curves for local recurrence (left) and distant metastases (right) NACT with no NACT (double column fitting image, in color).

obvious advantage of NACT over neoadjuvant re-irradiation is the systemic effect, which might be of extra importance in an aggressive malignancy such as angiosarcoma since distant metastases are possibly eradicated in an early stage. Downsides of neoadjuvant re-irradiation are the increased chance of wound infections, delayed wound healing, and late side effects of re-irradiation such as fibrosis which may affect the quality of life of the patient [29,30]. Both in the Mayo clinic and Cleveland clinic studies, high numbers of wound infections were observed, although in our study this was seen in 33.3 %. This can be due to the somewhat higher re-irradiation dose that was given in the Mayo

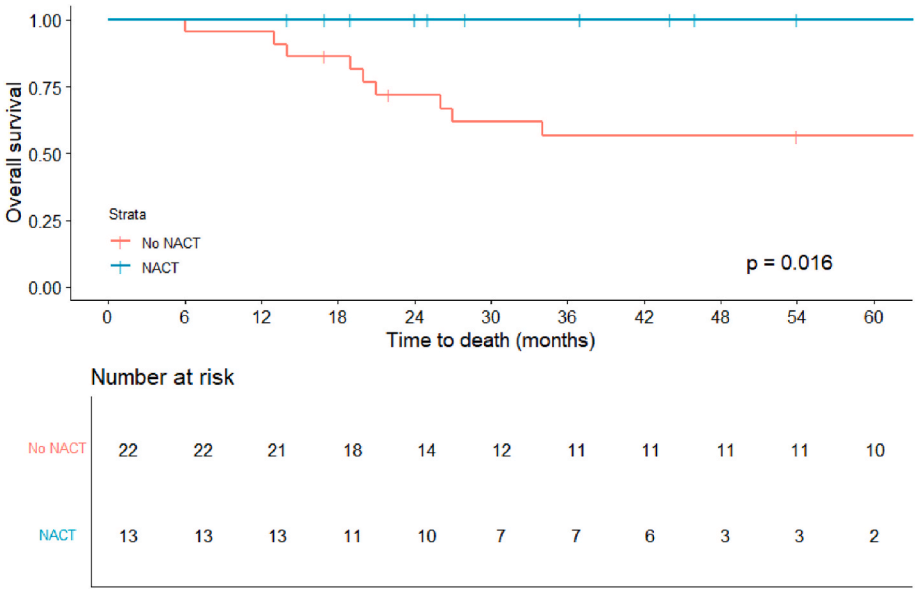



**Fig. 4.** Kaplan-Meier curve with overall survival, since start of first treatment, comparing NACT with no NACT. (single column fitting image, in color).

clinic and Cleveland clinic. If hyperthermia is added a lower total re/irradiation dose is given, since hyperthermia enhances the radiation effect in cancer cells. In breast cancer, NACT is not associated with more wound infections [31]. We hypothesize that NACT with taxanes couldbe standard of care in RAAS, while neoadjuvant re-irradiation with hyperthermia could be added on a case-by-case basis in more extensive disease, no or partial response to NACT or in the adjuvant setting in case of positive or very close resection margins. Of note, our study shows that clinical, radiological or metabolic response evaluation appears to underestimate pathological response, although the numbers are too small to do statistical analysis to prove this.

In order to test our hypothesis, we propose to conduct a larger prospective study to strengthen the results observed in this cohort. This study could include the prognostic value of clinical, radiological and metabolic response assessments, as well as molecular characteristics such as mitotic count and C-MYC amplification [32–34]. Both molecular characteristics were poorly documented in our cohort and therefore not included. Multiple shortcomings in this study have to be acknowledged. First of all, due to the rarity of the disease and especially this subtype of this specific anatomical site, the number of included patients is small. This prohibited most statistical tests from being significant, although, the differences were still clear. Correction for confounders was not possible either, but patient characteristics between the two groups appeared to be similar. Due to the retrospective set up, treatment was not exactly the same for all patients within the two groups and no quality of life was assessed. Furthermore, patients receiving NACT were all treated more recently, which means these patients also potentially benefited from generally more developed surgical and diagnostic methods and more frequent clinical visits for follow up.

## 5. Conclusion

In this single center, retrospective study, no patients treated with with neo-adjuvant taxanes for radiation associated angiosarcoma of the breast developed a recurrence, metastasis or died in the first three years. This suggests a positive impact of NACT for this rare disease. Larger and prospective studies are necessary to validate the effectiveness of NACT and further determine the role of neoadjuvant re-irradiation.

## CRediT authorship contribution statement

**Stijn J.C. van der Burg:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sophie J.M. Reijers:** Writing – review & editing, Validation, Data curation. **Anke Kuijpers:** Writing – review & editing. **Lotte Heimans:** Writing – review & editing. **Astrid N. Scholten:** Writing – review & editing, Validation, Conceptualization. **Rick L.M. Haas:** Writing – review & editing. **Hester van Boven:** Writing – review & editing. **Willemijn M. Kolff:** Writing – review & editing, Validation, Investigation, Data curation. **Marie-Jeanne T.F.D. Vrancken Peeters:** Data curation, Supervision, Validation. **Martijn Kerst:** Writing – review & editing. **Beatrijs A. Seinstra:** Writing – review & editing. **Neeltje Steeghs:** Writing – review & editing. **Winette T. A. van der Graaf:** Writing – review & editing, Conceptualization. **Yvonne M. Schrage:** Writing – review & editing, Supervision, Conceptualization. **Winan J. van Houdt:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization.

## Ethical approval

This study was approved by the local ethical committee (IRBd24-107, 04-04-2024).

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT in order to improve language and readability. After using this tool, the author reviewed and edited the content as needed and take full responsibility for the content of the publication.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

N. Steeghs provided consultation or attended advisory boards for Boehringer Ingelheim, Ellipses Pharma, GlaxoSmithKline, Incyte, Luszana. N Steeghs received research grants from Abbvie, Actuate Therapeutics, Amgen, Array, Ascendis Pharma, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Cantargia, CellCentric, Cogent Biosciences, Cresecendo Biologics, Cytovation,

Deciphera, Dragonfly, Eli Lilly, Exelixis, Genentech, GlaxoSmithKline, IDRx, Immunocore, Incyte, InteRNA, Janssen, Kinnate Biopharma, Kling Biotherapeutics, Lixte, Luszana, Merck, Merck Sharp & DohmeMerck Sharp & Dohme, Merus, Molecular Partners, Navire Pharma, Novartis, Numab Therapeutics, Pfizer, Relay Pharmaceuticals, Revolution Medicin, Roche, Sanofi, Seattle Genetics, Taiho, Takeda. All outside the submitted work, all payment to the Netherlands Cancer Institute.

W. van der Graaf: Advisory boards SpringworkTx, Agenus and PTC Therapeutics (all to the institute) and research grants from Eli Lilly (to the Institute). W. van Houdt: advisory boards of Amgen, Boehringer Ingelheim, Sanofi, Novartis, Sirius Pintuition, Belpharma. All payment to the Netherlands Cancer Institute.

## References


[1] Reijers SJM, Huis In 't Veld EA, Grünhagen DJ, Smith MJF, van Ginhoven TM, van Coevorden F, et al. Prognosis of patients with cutaneous angiosarcoma after surgical resection with curative intent: is there a difference between the subtypes? Ann Surg Oncol 2023;30(1):493–502.

[2] Fayette J, Martin E, Piperno-Neumann S, Le Cesne A, Robert C, Bonvalot S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol 2007;18 (12):2030–6.

[3] An R, Men XJ, Ni XH, Wang WT, Wang CL. Angiosarcoma of the breast: a review. Heliyon 2024;10(3):e24413.

[4] Kwapnoski Z, Clarey D, Ma J, Schmidt CM, Wysong A. Cutaneous angiosarcoma subtypes: a quantitative systematic review of demographics, treatments, and outcomes within published patient-level cases. Dermatol Surg 2024;50(7). 620-226.

[5] Rombouts AJM, Huising J, Hugen N, Siesling S, Poortmans PM, Nagtegaal ID, de Wilt JHW. Assessment of radiotherapy-associated angiosarcoma after breast cancer treatment in a Dutch population-based study. JAMA Oncol 2019;5(2):267–9.

[6] Cuperus E, Leguit R, Albregts M, Toonstra J. Post radiation skin tumors: basal cell carcinomas, squamous cell carcinomas and angiosarcomas. A review of this late effect of radiotherapy. Eur J Dermatol 2013;23(6):749–57.

[7] Virgilio E, Lombardi M, Stefano DD, Marchetti P, Cavallini M, Chieco PA. Angiosarcoma of the breast: a rare and dismal complication of breast surgery associated with radiation. Am Surg 2017;83(3):e71–3.

[8] Bonito FJP, de Almeida Cerejeira D, Dahlstedt-Ferreira C, Oliveira Coelho H, Rosas R. Radiation-induced angiosarcoma of the breast: a review. Breast J 2020;26 (3):458–63.

[9] Torres KE, Ravi V, Kin K, Yi M, Guadagnolo BA, May CD, et al. Long-term outcomes in patients with radiation-associated angiosarcomas of the breast following surgery and radiotherapy for breast cancer. Ann Surg Oncol 2013;20(4):1267–74.

[10] Mentzel T, Schildhaus HU, Palmedo G, Büttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol 2012;25(1):75–85.

[11] Salminen SH, Sampo MM, Böhling TO, Salo J, Tarkkanen M, Blomqvist CP, Hukkinen K. Radiation-associated angiosarcoma of the breast: analysis of diagnostic tools in a registry-based population. Acta Radiol 2022;63(1):22–7.

[12] Chen D, Tang M, Lv S, Wang H, Du W, Zhao X, et al. Prognostic usefulness of clinical features and pretreatment (18)F-FDG PET/CT metabolic parameters in patients with angiosarcoma. Quant Imaging Med Surg 2022;12(5):2792–804.

[13] Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol 2021;32(11):1348–65.

[14] Li GZ, Fairweather M, Wang J, Orgill DP, Bertagnolli MM, Raut CP. Cutaneous radiation-associated breast angiosarcoma: radicality of surgery impacts survival. Ann Surg 2017;265(4):814–20.

[15] Ghareeb ER, Bhargava R, Vargo JA, Florea AV, Beriwal S. Primary and radiation-induced breast angiosarcoma: clinicopathologic predictors of outcomes and the impact of adjuvant radiation therapy. Am J Clin Oncol 2016;39(5):463–7.

[16] Linthorst M, van Geel AN, Baartman EA, Oei SB, Ghidey W, van Rhoon GC, van der Zee J. Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall. Strahlenther Onkol 2013;189(5):387–93.

[17] Degnim AC, Siontis BL, Ahmed SK, Hoskin TL, Hieken TJ, Jakub JW, et al. Trimodality therapy improves disease control in radiation-associated angiosarcoma of the breast. Clin Cancer Res 2023;29(15):2885–93.

[18] Asha W, Al-Hilli Z, Djohan R, Budd GT, Obi E, Fleming-Hall E, et al. Neoadjuvant reirradiation for radiation therapy-associated angiosarcoma of the breast. Int J Radiat Oncol Biol Phys 2024;119(4):1082–5.

[19] Heinhuis KM, Ns IJ, van der Graaf WTA, Kerst JM, Schrage Y, Beijnen JH, et al. Neoadjuvant systemic treatment of primary angiosarcoma. Cancers 2020;12(8).

[20] Oxenberg J, Khushalani NI, Salerno KE, Attwood K, Kane JM. 3rd. Neoadjuvant chemotherapy for primary cutaneous/soft tissue angiosarcoma: determining tumor behavior prior to surgical resection. J Surg Oncol 2015;111(7):829–33.

[21] Kronenfeld JP, Crystal JS, Ryon EL, Yadegarynia S, Chitters C, Yechieli R, et al. Clinical outcomes for primary and radiation-associated angiosarcoma of the breast with multimodal treatment: long-term survival is achievable. Cancers 2021;13(15).

[22] Constantinidou A, Sauve N, Stacchiotti S, Blay JY, Vincenzi B, Grignani G, et al. Evaluation of the use and efficacy of (neo)adjuvant chemotherapy in angiosarcoma: a multicentre study. ESMO Open 2020;5(4).

[23] DeMartelaere SL, Roberts D, Burgess MA, Morrison WH, Pisters PW, Sturgis EM, et al. Neoadjuvant chemotherapy-specific and overall treatment outcomes in patients with cutaneous angiosarcoma of the face with periorbital involvement. Head Neck 2008;30(5):639–46.

[24] Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol 2008;26(32):5269–74.

[25] Depla AL, Scharloo-Karels CH, de Jong MAA, Oldenborg S, Kolff MW, Oei SB, et al. Treatment and prognostic factors of radiation-associated angiosarcoma (RAAS) after primary breast cancer: a systematic review. Eur J Cancer 2014;50(10): 1779–88.

[26] Abdou Y, Elkhanany A, Attwood K, Ji W, Takabe K, Opyrchal M. Primary and secondary breast angiosarcoma: single center report and a meta-analysis. Breast Cancer Res Treat 2019;178(3):523–33.

[27] Smith TL, Morris CG, Mendenhall NP. Angiosarcoma after breast-conserving therapy: long-term disease control and late effects with hyperfractionated accelerated re-irradiation (HART). Acta Oncol 2014;53(2):235–41.

[28] Sharon CE, Straker RJ, Shannon AB, Shabason JE, Zhang PJL, Fraker DL, et al. Neoadjuvant radiation for cutaneous and soft tissue angiosarcoma. J Surg Oncol 2022;125(3):509–15.

[29] Abdallah ZK, El Masry AM, Azmy SI, El Mowafi MA, Rahman Mustafa MA. Assessment of local complications with preoperative versus postoperative radiotherapy in patients with soft tissue sarcoma in extremities: a randomized comparative clinical trial. J Orthop 2024;53:34–40.

[30] Moore J, Isler M, Barry J, Mottard S. Major wound complication risk factors following soft tissue sarcoma resection. Eur J Surg Oncol 2014;40(12):1671–6.

[31] Decker MR, Greenblatt DY, Havlena J, Wilke LG, Greenberg CC, Neuman HB. Impact of neoadjuvant chemotherapy on wound complications after breast surgery. Surgery 2012;152(3):382–8.

[32] Chang HY, Dermawan JK, Kuba MG, Crago AM, Singer S, Tap W, et al. Clinicopathologic and molecular correlates to neoadjuvant chemotherapy-induced pathologic response in breast angiosarcoma. Genes Chromosomes Cancer 2024;63 (5):e23240.

[33] Abada E, Jang H, Kim S, Ali-Fehmi R, Bandyopadhyay S. A clinicopathologic and immunohistochemical study of primary and secondary breast angiosarcoma. J Pathol Transl Med 2022;56(6):342–53.

[34] Naka N, Ohsawa M, Tomita Y, Kanno H, Uchida A, Myoui A, Aozasa K. Prognostic factors in angiosarcoma: a multivariate analysis of 55 cases. J Surg Oncol 1996;61 (3):170–6.