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Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall

Introduction

Radiation induced angiosarcoma (RAS) of the chest wall/breast is one of the most aggressive types of tumor that can develop in an irradiated area after breast conserving therapy (BCT) [19, 25, 31, 39, 40]. It constitutes less than 1% of all breast cancers [39]. RAS is thus a relatively rare complication of BCT, but its incidence is likely to increase as more women undergo this treatment [12, 24, 32]. In three published series, the median times between BCT and RAS diagnosis were 59, 91 and 74 months [6, 7, 8]. Most cutaneous angiosarcomas are not amenable to surgical resection and a number of patients show metastases at diagnosis or develop them shortly after [1]. The prognosis of RAS patients is poor and the reported 5-year overall survival (OS) rate varies from 10 to 38% [9, 13, 39]. The most common cause of death is local progression along the chest wall [9]. Establishment of local control (LC) is thus important for preventing distressing symptoms [27]. The occurrence of RAS in a previously irradiated field limits the therapeutic options. In many cases, surgery is unfeasible and even after obtaining negative margins by simple mastectomy, additional local tumors recur in approximately 70% of patients (29–100%) [3, 7, 13, 16, 20, 23, 28, 29]. Full-dose re-irradiation is usually not possible and re-irradiation alone does not improve survival rate [21]. Re-irradiation plus hyperthermia (reRT + HT) is an effective treatment for recurrent breast cancer with acceptable toxicity. Results from five randomized trials have shown that the complete response (CR) rate for breast cancer recurrences increases from 41 to 59% when hyperthermia is combined with radiotherapy [36]. Multimodal therapies comprising surgery and reRT + HT may improve local tumor control in the treatment of angiosarcoma [26].

In an attempt to improve LC rates, we have treated RAS patients with a combination of surgery wherever this was feasible, and reRT + HT. Results of a retrospective analysis are reported here.

Materials and methods

Patient characteristics

Between 2000 and 2011, 24 patients with pathologically confirmed RAS of the chest wall underwent surgery where feasible, and reRT + HT. Hyperthermia treatments were applied in the Erasmus MC-Daniel den Hoed Cancer Center (DHCC, *n*=21) and the Bernard Verbeeten Institute (BVI, *n*=3). Of the 24 patients, 23 had been treated for primary breast cancer by modified radical mastectomy followed by either radiotherapy (*n*=4) or BCT (*n*=19). One patient had been treated for axillary melanoma. RAS presentation varied and included purple cutaneous discoloration, eczematous rash, swelling of the breast and regional lymphadenopathy [22]. In all cases, the RAS diagnosis had been confirmed pathologically. Patient and tumor characteristics are summarized in **Tab. 1.**

Treatment characteristics

Surgery

Surgery is the first choice of treatment for angiosarcoma and was performed wherever feasible. The surgery was scored an "R0 resection" if no microscopic tumor was found at the margin. An "R1 resection" indicates a microscopically positive margin after an otherwise complete resection and "R2 resection" indicates gross residual disease left behind after mastectomy.

Radiotherapy

Following surgery or recurrence confirmed by biopsy, patients received elective external beam radiation weekly. Radiotherapy was administered in 2–5 Gy

Tab. 1 Characteristics of patients and tumors (*n*=24)

Patient number	Previous surgery	Primary radiotherapy dose (Gy)	EQD2 (α/β=2) (Gy)	Boost (Gy)	Age[a]	Tumor maximum diameter (mm)	Depth (mm)	Metastases	Interval[b]
1	Mastectomy	46	46	0	66	0	30	No	47
2	Mastectomy	47.3	47	0	61	80	25	No	134
3	BCT	50	50	20	72	0	25	No	68
4	Mastectomy	45	51	0	46	22	30	No	118
5	BCT	52	52	0	68	85	30	Yes	69
6	Mastectomy	50	50	10	88	78	30	No	45
7	BCT	50	50	16	75	292	30	No	77
8	LND	40	60	0	79	300	30	No	113
9	BCT	50	50	16	68	0	30	No	136
10	BCT	50	50	20	50	0	40	No	68
11	BCT	50	50	16	76	90	30	No	120
12	BCT	50	50	0	72	40	30	No	106
13	BCT	50.68	48	13.72	57	340	30	No	52
14	BCT	50	50	0	76	0	30	No	154
15	BCT	50	50	16	72	0	30	No	71
16	BCT	50	50	16	79	150	30	No	95
17	BCT	50	50	16	84	60	30	No	103
18	BCT	50	50	20	73	0	30	No	98
19	BCT	50	50	16	63	9	30	Yes	58
20	BCT	50	50	16	64	13	40	Yes	66
21	BCT	50	50	16	82	80	30	No	212
22	BCT	50	50	16	68	100	30	No	202
23	BCT	50.68	48	13.72	57	190	30	No	70
24	BCT	50	50	26	74	0	30	No	53

EQD2 equivalent dose in 2 Gy fractions, *BCT* breast conserving therapy, *LND* lymph node dissection [a]Age in years at diagnosis of angiosarcoma [b]Interval in months between primary radiotherapy and angiosarcoma [c]Surgery after radiotherapy and hyperthermia.

fractions up to a total dose of 32–54 Gy (mean: 35 Gy), depending on previous therapy and tumor dimensions, or at the discretion of the radiation oncologist. All patients had received prior irradiation and were treated using a radiation technique comprising photons (6–15 MV linear accelerators), electrons (6–10 MeV) or a mixture of photons and electrons. Type and energy of the radiation beam, as well as the particular application method varied depending on the clinical situation. Patients received re-irradiation to the chest wall, breast, reconstructed breast and/or regional nodes. The planning target volume (PTV) for radiation therapy included the clinical target volume (CTV) plus a margin of 1 cm. PTV could be defined for 8 patients and varied from 0.52 to 6.13 dm^3 (median: 1.35 dm^3). The field size for radiation therapy included the recurrent tumor with a generous margin or the entire ipsilateral chest wall. Field size ranged from 175 to 1125 cm^2 (median: 444 cm^2) [17, 30, 38].

Hyperthermia

Hyperthermia treatments at DHCC were given once a week following the radiotherapy, for a total of four treatments. Hyperthermia was delivered using Lucite cone applicators and a 433 MHz technique, as previously described [2, 4]. The applicator setup was chosen to heat the whole re-irradiation volume [35]. At BVI, hyperthermia treatments were given twice a week for a total of six sessions. Hyperthermia was delivered using contact flexible microstrip applicators (CFMA) operating at 434 MHz [10, 15]. Treatment fields covered at least the area of surgery or recurrent tumor. For treatment areas too large to be covered by one applicator setup (those exceeding 20 by 30 cm^2), the treatment was carried out in two applications. Hyperthermia field size ranged from 200 to 1200 cm^2 (median: 600 cm^2). The hyperthermia treatment was given after the radiotherapy fraction on the same day. The aim of the treatment is to maintain all interstitial temperatures between 40 and 43°C [5]. At DHCC, surface temperature control was performed using a perfused water bolus, with the temperature depending on various applicator arrays and target depths [34]. At BVI, the water bolus temperature was usually set at 42°C. The standard prescribed duration of treatment was 60 min. This included a heating-up period of 10 min, during which the temperatures were increased homogeneously to values as high as patients' tolerance and normal tissue temperatures permitted (max. 44°C). Temperatures were either measured interstitially and on the skin (*n*=18), or only on the skin (*n*=6).

Endpoints

The primary endpoint of this study was defined by the duration of local control (DLC). DLC was defined as the time between the start of treatment (surgery or radiotherapy) and the first observation of progression within the re-irradiation field, made on either the day of death or at the

last follow-up examination. Secondary endpoints were CR and acute or late toxicity due to either re-irradiation or hyperthermia. Patients with persistent locoregional disease at the end of treatment had local failure (F) at time zero. Toxicity observed during or within 24 h after completion of a hyperthermia session was considered to be hyperthermia induced toxicity. All toxicity was scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [33]. Only the maximum grade recorded was included in the analysis.

Temperature parameters

Using the interstitial temperature data, various dose parameters were calculated. These included: the maximum (Tmax) and the average temperature (Tave) that was recorded over all temperature probes during the steady state period of each heating session (beginning 10 min after the start of heating); the temperature exceeded by 90% of all temperature probes during the steady state (T90) and the thermal isoeffect dose expressed in cumulative equivalent minutes at a reference temperature of 43°C, based upon the temporal development of T90 in the target (CEM43°CT90). For this analysis, the mean values of Tmax, Tave and T90 temperatures were used. The formulation for CEM43°CT90 used in this study has been previously described and used extensively [6, 11, 14].

Statistical analysis

Kaplan–Meier analysis was performed for DLC and OS duration. Univariate Cox regression was used to investigate which parameters were associated with LC and toxicity. For all calculations, p-values less than 0.05 were considered significant. For analysis, the Stata Statistical Software, release 11 was used (StataCorp, 2009).

Results

Median age was 70 years, with a range of 46 to 88 years. The 3-month, 1- and 3-year OS rates for the entire patient group were 91, 45 and 11%, respectively. After diagnosis of RAS, the duration of the follow-up period ranged from 1 to 78 months, with a median of 12 months. Surgery was per-

Abstract · Zusammenfassung

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Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall

Abstract

Purpose. Radiation-induced angiosarcoma (RAS) of the chest wall/breast has a poor prognosis due to the high percentage of local failures. The efficacy and side effects of re-irradiation plus hyperthermia (reRT + HT) treatment alone or in combination with surgery were assessed in RAS patients.

Patients and methods. RAS was diagnosed in 23 breast cancer patients and 1 patient with melanoma. These patients had previously undergone breast conserving therapy (BCT, n=18), mastectomy with irradiation (n=5) or axillary lymph node dissection with irradiation (n=1). Treatment consisted of surgery followed by reRT + HT (n=8), reRT + HT followed by surgery (n=3) or reRT + HT alone (n=13). Patients received a mean radiation dose of 35 Gy (32–54 Gy) and 3–6 hyperthermia treatments (mean 4). Hyperthermia was given once or twice a week following radiotherapy (RT).

Results. The median latency interval between previous radiation and diagnosis of RAS was 106 months (range 45–212 months). Following reRT + HT, the complete response (CR) rate was 56%. In the subgroup of patients receiving surgery, the 3-month, 1- and 3-year actuarial local control (LC) rates were 91, 46 and 46%, respectively. In the subgroup of patients without surgery, the rates were 54, 32 and 22%, respectively. Late grade 4 RT toxicity was seen in 2 patients.

Conclusion. The present study shows that reRT + HT treatment—either alone or combined with surgery—improves LC rates in patients with RAS.

Keywords

Survival rate · Radiotherapy · Breast cancer · Toxicity · Mastectomy

Wirkung einer Kombination aus chirurgischer Therapie, erneuter Bestrahlung und Hyperthermie auf die lokale Kontrollrate bei strahleninduzierten Angiosarkomen der Brustwand

Zusammenfassung

Ziel. Das strahleninduzierte Angiosarkom (RAS, „radiation-induced angiosarcoma“) der Brustwand hat wegen des hohen Anteils an lokalem Versagen eine schlechte Prognose. Die Wirksamkeit und Nebenwirkungen von Rebestrahlung und Hyperthermie (ReRT + HT) allein oder in Kombination mit vorhergehender oder nachfolgender Operation wurden bei Patienten mit einem RAS der Brustwand überprüft

Patienten und Methoden. RAS wurde bei 23 Patientinnen mit Brustkrebs und bei einer Patientin mit malignem Melanom, nach früherer brusterhaltender Brustkrebstherapie (n=18), Mastektomie mit Bestrahlung (n=5) und axillärer Lymphknotendissektion mit Bestrahlung (n=1) diagnostiziert. Die Behandlung des RAS bestand aus Chirurgie gefolgt von ReRT + HT (n=8), ReRT + HT gefolgt von Chirurgie (n=3) oder ReRT + HT allein (n=13). Die Patienten wurden mit einer Strahlendosis von 32–54 Gy behandelt (durchschnittlich 35 Gy) und 3–6 Hyperthermiebehandlungen (durchschnittlich 4). Die Hyperthermie wurde 1-mal oder 2-mal pro Woche nach der Bestrahlung gegeben.

Ergebnisse. Das durchschnittliche Latenzzeitintervall zwischen ehemaliger Bestrahlung und RAS-Diagnose betrug 106 Monate (Bereich 45–212 Monate). Nach ReRT + HT lag die komplette Remission (CR) bei 56%. In der Untergruppe von Patienten mit Chirurgie lagen die 3-Monats-, 1- und 3-Jahres-Lokalkontrollraten (LC) bei 91%, 46% und 46%. In der Untergruppe von Patienten ohne Operation waren dies 54%, 32% und 22%. Eine Grad-4-Spättoxizität zeigte sich bei 2 Patienten.

Schlussfolgerung. Die vorliegende Studie zeigt, dass ReRT + HT entweder allein oder in Kombination mit Chirurgie zu einer verbesserten LC-Rate bei Patienten mit RAS führt.

Schlüsselwörter

Überlebensrate · Radiotherapie · Brustkrebs · Toxizität · Mastektomie

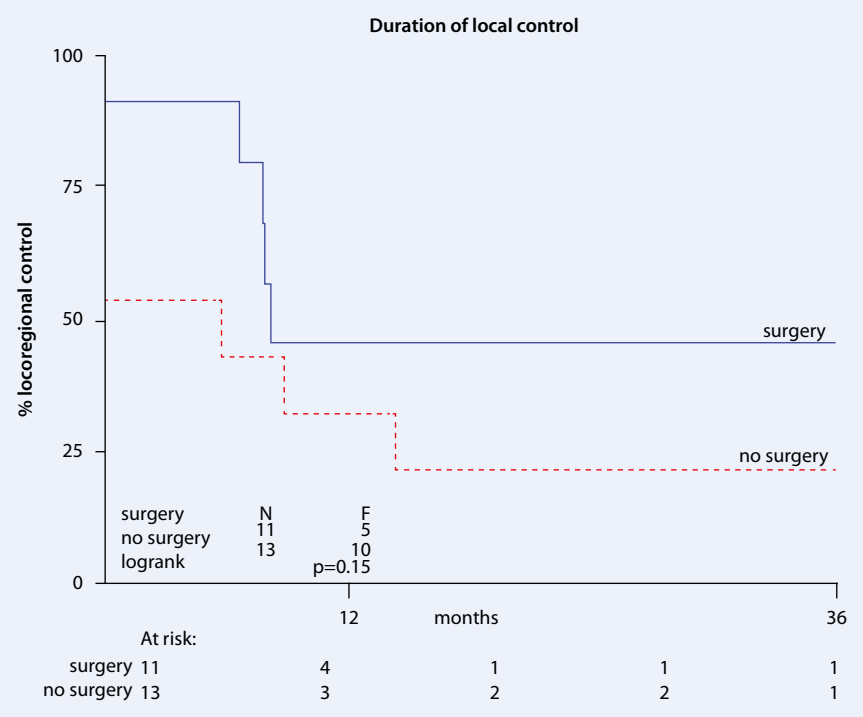

Fig. 1 ▲ Duration of local control for patients undergoing surgery versus no surgery. *N* number, *F* failure

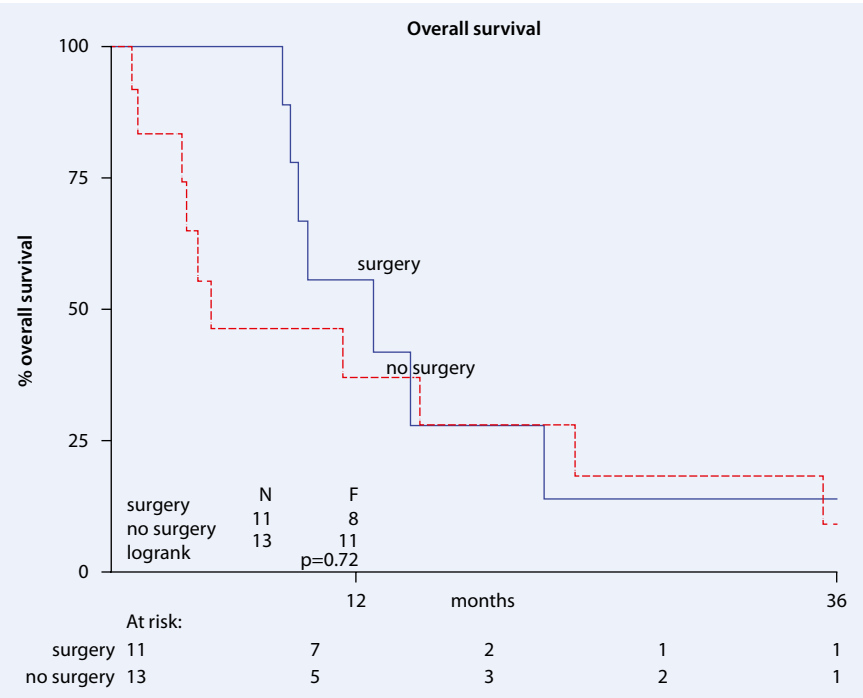

Fig. 2 ▲ Overall survival for patients with surgery versus no surgery. *N* number, *F* failure

formed on 11 patients (46%). Of these 11 patients, 3 underwent radiotherapy preoperatively and 8 postoperatively. The remaining 13 patients received reRT + HT alone.

Tumor response and local control

All patients were eligible for response evaluation (**Tab. 2**). At the completion of reRT + HT treatment in 16 patients with measurable tumors—excluding the 8 patients with microscopic disease—9 patients (56%) exhibited CR, 4 (25%) partial response, 2 (13%) showed no change and 1 (6%) had progressive disease. In one patient who had received surgery after reRT + HT, a pathological CR was achieved. Including the patients with microscopic disease, 3-month, 1- and 3-year LC rates were 71, 38 and 29%,respectively. Median DLC was 8 months (range: 2–52 months). In the surgery group, 3-month, 1- and 3-year LC rates were 91, 46 and 46%, respectively. Recurrence on the chest wall between 7 and 8 months was observed in 4 patients. In the no-surgery group, 3-months, 1- and 3-year LC rates were 54, 32 and 22%, respectively and 4 patients had a recurrence on the chest wall between 6 and 51 months. These results are presented in **Fig. 1.**

Prognostic factors

We assessed several factors for their prognostic significance regarding DLC using univariate analysis (**Tab. 3**). None of the parameters showed a significant correlation with DLC, presumably due to the small number of patients included in the study.

Survival

The median latency interval between previous radiation and diagnosis of RAS was 106 months (range: 45–212 months). The median survival time after reRT + HT for all 24 patients was 12 months (range: 1–78 months). The median survival time following RAS diagnosis was 18 months (range: 2–79 months). Patients who had undergone surgery (median survival: 13 months, range: 1–51 months) showed a trend toward better survival rates compared to patients who received reRT + HT alone (median survival: 5 months, 1–78 months), but this was not statistically significant (p=0.719, **Fig. 2**). The 4 patients treated by complete resection and the 7undergoing incomplete resection had median survival times of 9 and 10 months, respectively.

At the last follow-up, 5 patients were still alive 1–8 months after the start of treatment (mean: 2 months); 1 had distant metastases and 1 had both local failure

Tab. 2 Characteristics and outcome of treatment (*n*=24)

Patient number	Radiotherapy dose (Gy)	EQD2 (α/β=2) (Gy)	Surgical treatment	Margins	No. of hyperthermia treatments	Tmax (°C)	Tave (°C)	T90 (°C)	CEM43T90 (min)	Outcome	DLC[a] (mo)	OS[a] (mo)
1	32	48	Excision	R1	4	43.8	41.8	40.6	1.70	CR	8	9
2	50	50	–	–	5	43.5	40.8	39.4	0.40	CR	9	15
3	32	48	Mastectomy	R1	4	43.2	41.3	40.2	1.33	CR	10	10
4	54	54	–	–	4	–	–	–	–	CR	51	78
5	32	48	–	–	4	43.6	40.9	39.0	0.23	NR	0	4
6	32	48	–	–	4	–	–	–	–	CR	6	12
7	32	48	–	–	4	43.0	40.4	38.7	0.13	CR	14	23
8	32	48	–	–	4	43.7	41.2	39.4	0.49	PD	0	5
9	32	48	Mastectomy	R1	4	43.6	41.4	40.0	0.78	CR	52	52
10	50	50	Mastectomy	R0	4	43.3	40.8	39.4	0.38	CR	8	21
11	32	48	–	–	3	42.7	39.6	37.8	0.28	PR	0	4
12	32	48	–	–	4	43.2	41.7	40.6	1.88	CR	35	35
13	40	60	Mastectomy[c]	R2[b]	4	43.3	41.4	39.4	0.46	PR	0	9
14	32	48	Mastectomy	R1	4	42.6	40.6	39.4	0.40	CR	13	13
15	36	54	Mastectomy	R1	4	–	–	–	–	CR	7	15
16	32	48	–	–	4	42.3	40.2	38.8	0.18	CR	4	4
17	32	48	–	–	4	42.6	41.3	40.4	3.93	NR	0	1
18	32	48	Mastectomy	R1	4	–	–	–	–	CR	10	10[c]
19	32	48	–	–	4	43.8	40.6	38.7	0.15	CR	3	3[c]
20	32	48	–	–	4	–	–	–	–	PR	0	1[c]
21	32	48	Mastectomy[c]	R0[b]	4	44.0	40.8	39.1	0.23	CR	2	2[c]
22	36	45	–	–	6	–	–	–	–	PR	0	1
23	36	45	Mastectomy[c]	R0[b]	5	37.3	38.2	36.5	–	CR	2	2[c]
24	36	45	Mastectomy	R0	6	39.3	41.0	37.8	–	CR	8	9

EQD2 equivalent dose in 2 Gy fractions,*Tmax* maximum steady state temperature, *Tave* average steady state temperature, *T90* steady state temperature exceeded by 90% of all probes, *CEM43T90* development of T90 at 43°C in cumulative equivalent minutes, *DLC* duration of local control, *OS* overall survival, *CR* complete response, *NR* no response, *PR* partial response, *mo* months, *min* minutes [a]Patients with local control or still alive at the date of last follow-up [b]Surgery after radiotherapy and hyperthermia [c]Still alive.

Tab. 3 Association of patient, tumor and treatment characteristics with duration of local control (DLC, *n*=24)

Parameter	HR	p-value
Radiotherapy dose (Gy)	0.95	0.634
Age[a] at diagnosis of angiosarcoma	1.01	0.673
Margin of operation (radical/irradical)	0.29	0.214
Interval between primary radiotherapy and angiosarcoma (mo)	0.99	0.225
Tumor diameter (mm)	1.00	0.427
Interval between primary radiotherapy and hyperthermia (mo)	0.99	0.233
Radiotherapy field size (cm^2)	1.00	0.318
T90 (°C)	0.75	0.388
Hyperthermia field size (cm^2)	1.00	0.400
Number of hyperthermia treatment sessions (3–4/5–6)	1.65	0.449
CEM43T90 (min)	1.08	0.855
Tmax (°C)	0.97	0.886
Tave (°C)	0.98	0.973

HR hazard ratio, *mo* months, *min* minutes, *Tmax* maximum steady state temperature, *Tave* average steady state temperature, *T90* steady state temperature exceeded by 90% of all probes, *CEM43T90* development of T90 at 43°C in cumulative equivalent minutes [a]Age in years at diagnosis of angiosarcoma.

and distant metastases. The 19 deaths occurred 1–77 months (median: 8 months) after commencement of treatment. Causes of death were locoregional recurrence (*n*=11), distant metastases (*n*=3) and a combination of both (*n*=5).

Toxicity

The duration of hospitalization for the surgical procedure in 11 patients varied between 3 and 12 days. Acute adverse effects from re-irradiation included moderate to pronounced erythema, dry desquamation (21%), and moist desquamation (13%). The effects were generally self-limiting and healed a few weeks after treatment. In one patient, acute grade 3 radiotherapy toxicity appeared after 2 months. This patient developed an infection and required wound debridement of the chest wall. Thermal blisters occurred in 6 patients. No subcutaneous burns were ob-

Tab. 4 Surgery, re-irradiation and hyperthermia

Reference	Patients (n)	Tx	Local tumor progression	Follow-up (mo)	OS (2yrs)	OS (5yrs)	LC (1yr)	LC (3yrs)	LC (5yrs)
Surgery									
Billings et al. [3]	23	WLE, M, RT, CT	14 (61%)	44 (12–91)	–	–	–	–	–
Jallali et al. [13]	13	7 complete M, WLE 6 incomplete M, WLE	6 (86%) 6 (100%)	15 (3–72) 15 (3–72)	42% 0%	10% 0%	– –	– –	– –
Lindford et al. [16]	9	M, WLE	3 (33%)	81 (4–122)	66%	66%	–	–	–
Monroe et al. [20]	75	M	55 (73%)	12 (no range)	–	–	–	–	–
Seinen et al. [29]	31	S	19 (29%)	27 (1–151)	32%	–	–	–	–
Surgery and reRT ± HT									
de Jong et al. [7]	3	S, reRT, HT	0	10 (8–68)	67%	67%	–	–	–
Currrent study	11	S, WLE, reRT, HT	4 (36%)	13 (4–51)	14%	0%	46%	46%	–
Palta et al. [23]	14	S, HART	4 (29%)	9	86%	86%	–	71% (2yrs)	64%
Scott et al. [28]	16	S, HART	1 (6%)	44(2–343)	85%	75%	–	–	92%
reRT + HT									
de Jong et al. [7]	13	reRT, HT	3 (23%)	12 (8–68)	23% (3yrs)	–	–	31%	–
Current study	13	reRT, HT	4 (31%)	11 (1–77)	19%	9%	32%	22%	–

reRT ± HT re-irradiation plus/minus hyperthermia, *reRT + HT* re-irradiation plus hyperthermia *Tx* treatment, *M* mastectomy, *WLE* wide local excision, *LND* lymph node dissection, *CT* chemotherapy, *HART* hyperfractionated and accelerated radiotherapy, *RT* radiotherapy, *reRT* re-irradiation, *HT* hyperthermia, *S* surgery, *com* complete, *income* incomplete, *OS* overall survival, *LC* local control, *mo* months, *yr(s)* year(s).

served. Grade 3 toxicity related to hyperthermia did not arise. Late grade 4 radiotherapy toxicity was seen in 2 patients, 7- and 11 months after the treatment. One of these patients developed osteoradionecrosis of the chest wall and required resection of this necrotic area. The other patient required debridement for a chronic wound.

Discussion

Secondary angiosarcomas have been associated with previous surgery, irradiation or long-standing extremity edema in Stewart–Treves syndrome [19]. As BCT has become the standard treatment for patients with noninvasive and early breast cancer, the development of post-BCT angiosarcoma has become a well-documented complication, with an incidence rate ranging from 0.05 to 1.11% [8, 18, 39]. This low incidence hinders conduction of large randomized studies on patients with angiosarcoma of the chest wall, and most available data has been determined from retrospective analyses (**Tab. 4**).

A total of 151 patients who had received surgery alone could be identified in the literature [3, 13, 16]. The local tumor progression rate was 68% with a period of 12–81 months (median: 21 months) to relapse. A total of 44 patients—including 11 from our series—received surgery plus radiotherapy (± hyperthermia) [7, 20, 28]. Response to treatment was observed for 46–92% of patients, with local recurrence in 20% after 8–19 months. One patient undergoing surgery after reRT + HT had a pathological CR following the combined therapy. In 26 patients, reRT + HT was the only treatment applied for an unresectable tumor. Local tumor progression occurred in 27% of patients after a follow-up of 1–77 months (median: 12 months). The 3-year LC rate was 22% in the current study and 31% in the study of de Jong et al. [7].

Radical surgery is not always possible. Seinen et al. [29] report that in 23 out of 31 patients who underwent surgery, the primary treatment resulted in R0 resections. Nevertheless, due to the multifocal growth of angiosarcoma and residual tumor tissue, nearly two-thirds of these patients developed a local recurrence, even if the surgical margins were considered free. Radical excision of RAS is important not only for long-term LC, but also for OS; Jalalli et al. [13] found median survival times of 42 and 15 months for patients who had complete and incomplete resection, respectively, and Lindford et al. [16] reported a median OS of 81 months for 9 patients in whom the tumor could be widely resected.

Combination therapy comprising surgery and re-irradiation seems to improve both LC and OS in comparison to patients treated by surgery alone. Palta et al. [23] reported an LC rate of 71%, 2 years after postoperative radiotherapy with a median dose of 60 Gy. Side effects included moist desquamation, which healed with antibacterial and antifungal agents within a few weeks. One patient developed recurrent pleural effusion 5 years after treatment. Scott et al. [28] reported 5-year LC and OS rates of 92% and 75%, respectively, among patients receiving postoperative hyperfractionated accelerated radiotherapy (HART) with 1 Gy given three times daily to a total dose of 60 Gy. No patients developed CTCAE grade 3 or more severe complications, despite a high cumulative dose of radiation. In the current study, postoperative hypofractionated reRT + HT resulted in a 1- and 3-year LC rate of 46%, which is lower than that reported by Palta et al. [23] and Scott et al. [28]. These differences may be due to patient selection criteria.

The limitations of the current study are its retrospective nature and the relatively small sample size, which preclude firm conclusions. Furthermore, it is difficult to compare the results with those of other studies and to establish the effect of hyperthermia. The outcome in the subgroup with a radiotherapy dose of 36–54 Gy (n=8) was a LC rate of 75%, with a median of 7 months (range: 0–51 months). In the subgroup of patients with a radiotherapy dose of 32 Gy (n=16), the LC rate was 69% for a duration of 0–52 months (median: 5 months, p=0.634). Late grade 4 tox-

icity developed in 2 patients; one in each subgroup.

Conclusion

Although the chest wall already has been irradiated in patients with RAS, re-irradiation is still possible and improves postoperative LC rates. The best published LC rates were achieved by combining surgery and HART. With the increasing incidence of angiosarcoma, a prospective study comparing different radiotherapy schemes with or without hyperthermia may be possible in the future. Initial treatment for angiosarcoma should be wide surgical resection (wherever feasible) followed by radiotherapy, which may be more effective when combined with hyperthermia. For initially inoperable tumors, the effect of reRT + HT alone can still be beneficial.

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