Lung Cancer 71 (2011) 338–343

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Definitive radiotherapy plus regional hyperthermia with or without chemotherapy for superior sulcus tumors: A 20-year, single center experience

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ARTICLE INFO

Article history:
Received 23 March 2010
Received in revised form 10 June 2010
Accepted 10 June 2010

Keywords:
Hyperthermia
Radiotherapy
Superior sulcus tumors
Non-small cell lung cancer
Pancoast tumor

ABSTRACT

Purpose: To assess the efficacy and toxicity of definitive radiotherapy (RT) plus regional hyperthermia (HT) in treating superior sulcus tumors (SSTs), and to identify predictors of positive outcomes.
Methods and materials: Twenty-four patients with SSTs treated with definitive RT plus regional HT were retrospectively analyzed. The median total dose of RT was 70 Gy. All patients were treated with an 8-MHz RF-capacitive heating device. Twelve of 24 (50%) patients also underwent chemotherapy. Those with either subcutaneous fat measuring 2.5 cm or greater, or any other serious complications did not undergo this therapy.
Results: Overall survival, local control, and distant metastasis-free survival rates at 3 years were 47%, 55%, and 71%, respectively. Chemotherapy and younger age (<65 years) were significant predictors of the overall survival rate. Clinical stage (IIB) was a statistically significant prognostic indicator for local control survival rate. Toxicities were mild, with Grade 3 dermatitis seen in one patient.
Conclusions: Definitive RT plus regional HT with chemotherapy may be a promising treatment for SSTs. The results justify further evaluation with detailed treatment protocols in a large number of patients.

1. Introduction

Lung cancers that occur in the apex of the chest and invade apical chest wall structures are called superior sulcus tumors (SSTs), or Pancoast tumors. SSTs, which are rarely encountered in clinical practice, represent <5% of all bronchogenic carcinomas [1]. The clinical syndrome is characterized by pain around the shoulder that can radiate to the axilla, toward the scapula, or down the arm, usually in an ulnar distribution. SSTs are also characterized by atrophy of the hand muscle and Horner's syndrome. These symptoms are due to involvement of the lower trunk of the brachial plexus. The close proximity of this critical structure to the tumor has often made SSTs unresectable. Although traditional management calls for radiotherapy (RT) followed by surgery, one study found that only 60% of patients could be completely resected, and overall survival was approximately 30% [2]. Recently, the addition of chemotherapy to preoperative RT (45 Gy) has improved both resectability and survival rates, with a complete resection in 68–78% of patients, and a 5-year survival rate of 44–56% [3,4].

Definitive RT with or without chemotherapy is another approach. The results of RT alone for SSTs are generally poor [5]. Selection bias tends to result in patients with more advanced disease or those who are poor surgical candidates. Nonetheless, a 5-year survival rate of 21–23% has been reported, indicating that this modality eradicates disease [6–8]. Komaki et al. used a multimodal approach to report outcome predictors in 143 patients with SSTs. Surgery was not a predictor of survival in patients with Stage IIIA (positive nodes) and Stage IIIB disease [9]. The published literature has not resolved this controversy due to bias in studies comparing definitive RT with preoperative irradiation and surgery.

Hyperthermia (HT) is known to be cytotoxic for cancer, and also acts as a radiation and chemosensitizer. Randomized phase III clinical trials have shown the efficacy of RT plus HT in patients with advanced head-and-neck cancer, locally recurrent breast carcinoma, malignant melanoma, and cervical cancer [10,11]. Some promising results have also been reported for RT plus regional HT

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doi:10.1016/j.lungcan.2010.06.007

for lung cancer [12–17]. A few small case series of patients with SSTs treated with RT plus HT [14,15] have been carried out. In a preliminary study from 1986 to 1989, we reported on 6 patients treated with definitive RT plus regional HT; the combined therapy was feasible and promising [14].

Multimodality therapy, including surgery, is not feasible for every patient who presents with SST. Kappers et al. demonstrated that only 30% of M0 patients with SST were eligible for combined modality treatment followed by surgery [18]. In patients with compromised health or unresectable disease, we hypothesized that definitive RT plus regional HT with or without chemotherapy may be a good alternative for surgery. This study was designed to update clinical results for SSTs treated with definitive RT plus regional HT, with or without chemotherapy, to assess efficacy and toxicity and to identify predictors of positive outcomes.

2. Methods and materials

2.1. Patients

From 1986 to 2007, 770 patients with primary non-small cell lung cancer (NSCLC) were seen in the Division of Therapeutic Radiology at our University Hospital. There were 30 patients (3.9%) with SSTs treated with RT plus regional HT. Preoperative or postoperative cases were excluded in this study; 6 patients with SSTs were treated with preoperative RT plus regional HT. We performed a retrospective analysis of 24 consecutive patients (23 males and one female; age range, 40–84 years; median age, 65 years) who had SST treated with definitive RT plus regional HT, with or without chemotherapy; 6 patients with SST who were previously reported were included [14]. The study was approved by the Institutional Review Board of the University of Occupational Health and Environmental Health.

All patients had pathologically confirmed NSCLC. Patients with subcutaneous fat of 2.5 cm or greater, which causes a decrease in the effectiveness of the radiofrequency-capacitive device, or other serious complications, such as severe pulmonary, cerebrovascular or renal diseases, did not undergo this therapy. Baseline characteristics and treatment of patients are listed in Tables 1 and 2. Although no specific chemotherapy protocol existed, 12 of 24 (50%) patients underwent chemotherapy. Four patients received induction chemotherapy as follows: intravenous administration of carboplatin plus paclitaxel; carboplatin plus gemcitabine; cisplatin plus vindesin; and bronchial arterial infusion of cisplatin. Nine patients underwent concurrent chemotherapy. Three received the intravenous administration of carboplatin in combination with paclitaxel, and two received bronchial arterial infusion of cisplatin. The others received the intravenous administration of carboplatin alone; cisplatin in combination with vindesin; and intraoral administration of uracil-tegafur or tegafur-gimeracil-oteracil potassium. Five patients received adjuvant chemotherapy after RT with HT, including intravenous carboplatin in combination with 5-fluorouracil; carboplatin plus paclitaxel; cisplatin in combination with vindesin; cisplatin in combination with 5-fluorouracil; and vinorelbine ditartrate alone.

Table 1
Patients characteristics.

Variable	No. (%)
Median age, years (range)	65 (40–84)
Gender	
Men	23 (96)
Women	1 (4)
Performance status	
1	14 (58)
2	10 (42)
Histologic type	
Adenocarcinoma	11 (46)
Squamous cell carcinoma	8 (33)
Large cell carcinoma	2 (8)
Others	3 (13)
Tumor, node, metastasis[a]	
IIB	8
T3N0M0	8 (33)
IIIA	2
T3N1M0	1 (4)
T3N2M0	1 (4)
IIIB	14
T2N3M0	1 (4)
T3N3M0	2 (8)
T4N0M0	6 (25)
T4N2M0	1 (4)
T4N3M0	4 (17)
Presenting symptom	
Chest pain, radiating down the arm and paresthesia/muscle weakness	6 (25)
Paresthesia/muscle weakness	5 (21)
Chest pain, radiating down the arm	2 (8)
Chest pain	2 (8)

[a] International Union Against Cancer tumor, node, metastasis classification, 5th edition.

Table 2
Treatment methods.

Treatment methods	No. (%)
Radiotherapy	
Median total dose (Gy)	70.2
Range (Gy)	55.2–83.4
Daily dose (Gy)	1.6–3.0
BED Gy10	
≧60 and <70 Gy10	1 (4)
≧70 and <80 Gy10	5 (21)
≧80 and <90 Gy10	11 (46)
≧90 Gy10	7 (29)
Hyperthermia	
Median times (range)	8 (2–20)
Thermometry	
Direct intra-tumor measurements	15 (63)
Intra-esophageal thermometry	1 (4)
Not measured	8 (33)
Chemotherapy	12 (50)
Induction chemotherapy	4 (17)
Concurrent chemotherapy	9 (38)
Adjuvant chemotherapy	5 (21)

BED, biologically effective dose.

2.2. Radiotherapy

All patients were treated with external RT using a 4, 6, or 10 MV linear accelerator. The median total dose was 70.2 Gy (range 55.2–83.4 Gy). The fractions ranged from 1.6 to 3.0 Gy once a day (five times/week) in 21 patients. Two daily fractions of 1.2–1.5 Gy with intervals of 6 h were administered to 3 patients. In the majority of patients, 40–50 Gy was administered through anterior–posterior portals encompassing the primary tumor plus regional lymph nodes with a margin. A 10–20 Gy boost dose was delivered to the tumor and enlarged lymph nodes using various techniques. Computed tomography-assisted three-dimensional treatment planning (FOCUS; CMS Japan, Tokyo, Japan) was used to determine the radiation fields in 13 (54%) of 24 patients between October 1995 and October 2007, with clinical target volume (CTV) defined as the pri-

mary lung tumor and regional lymph nodes. The planning target volume (PTV) included the CTV plus a 1–2 cm margin for daily set-up variation. The biologically effective dose (BED) can be used to compare the efficacy of various dose-fractionation regimens in providing tumor control [19,20]. The BED (total dose) × (1 + daily dose/[α/β]) using a linear quadratic model with α/β ratios of 10 ranged from 68.2 to 104.0 Gy_{10} (median, 84.0 Gy_{10}; Table 2).

2.3. Hyperthermia

HT was applied within 15 min after RT once or twice a week. The heat was applied using an 8-MHz radiofrequency-capacitive regional HT (Thermotron RF-8, Yamamoto Vinita Co., Osaka, Japan). The number of treatments ranged from 2 to 20 (median 8). The physical features of the Thermotron RF-8 clinical HT machine and thermal distribution have been previously reported in a phantom and human body [21–23]. The upper electrode was 14–30 cm; the lower was 21–30 cm in diameter, placed on opposite sides of the apical portion of the lung. The patients were treated in a supine or prone position. Heating duration was 40–70 min (median 50). The goal of heating was to continue the treatment for least 30 min after radiofrequency output was increased to the patient's tolerance threshold. Patients were carefully instructed to mention any unpleasant sensation suggestive of a hot spot. The radiofrequency output was increased to the maximum level tolerated by the patient after appropriate adjustments of the treatment setting. To reduce preferential heating of subcutaneous fat tissue, overlay boluses were applied in addition to regular boluses attached in front of the metal electrodes.

We directly measured intra-tumor temperature in 16 patients, and intra-esophageal temperature in one using a four-point microthermocouple sensor. We took measurements either one ($n = 15$) or two ($n = 1$) times. The sensor was inserted into the tumor through a 21-gauge catheter, or into the esophagus at the level of the tumor. The remaining 8 patients were not measured for temperature. Thermometric parameters measured included minimum (T_{min}), maximum (T_{max}), and mean (T_{ave}) temperature during the steady-state and at the end of treatment. The steady-state was defined as 20 min after the start of HT. We also measured the proportion of total HT time when at least one of the four measurements was 41 °C or higher (%$T \geqq 41$ °C).

2.4. Evaluation of tumor response and toxicity

The objective tumor response was evaluated by measuring the tumor size mainly by CT before RT, and 1–2 months after. Treatment response was evaluated according to World Health Organization criteria [24]. A complete response (CR) was defined as complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was a reduction in tumor size of at least 50%. Progressive disease (PD) was defined as a 25% increase in measurable lesions or the appearance of any new measurable or nonmeasurable lesion. Patients who did not meet the definitions of response or progression were classified as having no change (NC). We evaluated the toxicity of therapy according to Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0. The highest toxicity for each patient during and after RT with HT was used for toxicity analysis. The toxicity was defined as either acute (during therapy and up to 3 months after therapy) or late (over 3 months after the completion of therapy).

2.5. Statistical analysis

Overall survival, local control, and distant metastasis-free survival rates were calculated from the start of RT using the Kaplan–Meier method. The statistical significance of the difference between the actuarial curves was assessed using the log-rank test. To identify prognostic factors, univariate analyses were performed using age, performance status, tumor size, histologic characteristics, tumor staging, total radiation dose (BED), the number of HT treatments with or without chemotherapy, and thermal parameters. Logistic regression analyses were used to compare objective tumor response (CR + PR) with thermal parameters. Multivariate analyses using the Cox proportional-hazards model were performed to determine the overall survivals between age and chemotherapy, and for also determining the local control rates among such factors as the performance status, stage, total radiation dose, hyperthermia and chemotherapy.

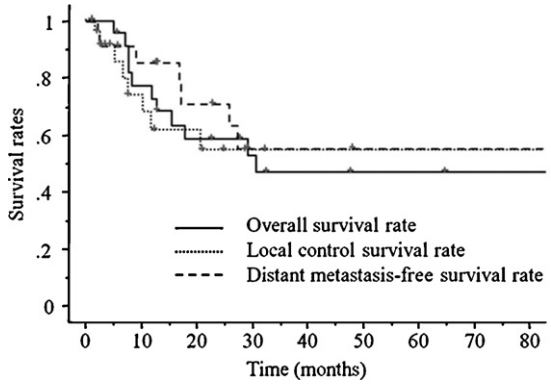

Fig. 1. Overall survival, local control survival, and distant metastasis-free survival of all patients.

3. Results

3.1. Objective tumor response and survival

The tumor response was PR in 12 patients, NC in 11, and PD in 1. The PR rate was 50%. Follow-up ranged from 2 to 145 months (median, 23 months). Overall survival, local control, and distant metastasis-free survival rates at 1 year were 73%, 62%, and 85%, respectively; at 3 years were 47%, 55% and 71%, and at 5 years, 47%, 55%, and 55%, respectively (Fig. 1). The initial sites of disease progression were local in 8 patients, distant in 5, and both in one.

Table 3 shows the univariate analysis for the three survival rates. Chemotherapy was a significant predictor for overall survival rate ($p = 0.004$) (Fig. 2a). Younger age (<65 years) was also a significant prognostic indicator for overall ($p = 0.033$) and distant metastasis-free survival rates ($p = 0.046$). Clinical Stage (IIB) was a statistically significant prognostic indicator for local control survival rate ($p = 0.049$) (Fig. 2b). None of the other factors showed a statistically significant association for local control survival rate, although trends toward significance were seen for total radiation dose ($\geqq 82$ Gy_{10}) ($p = 0.074$) and hyperthermia ($\geqq 8$ times) ($p = 0.082$) (Fig. 2c and d). The interaction of the overall survival with chemotherapy was significant according to the multivariate analyses ($p = 0.03$), while that of the overall survival with age was not significant ($p = 0.16$). Regarding the local control rate based on multivariate analyses, none of the predictive factors for the performance status, stage, total radiation dose, hyperthermia or chemotherapy were significant.

3.2. Thermometry results

The T_{max} in the 16 patients who underwent measurement of tumor temperature ranged from 39.1 °C to 47.1 °C, with a median 42.6 °C. The T_{min} ranged from 38.7 °C to 46.7 °C, with a median 41.3 °C. The T_{ave} ranged from 38.8 °C to 46.8 °C, with a median

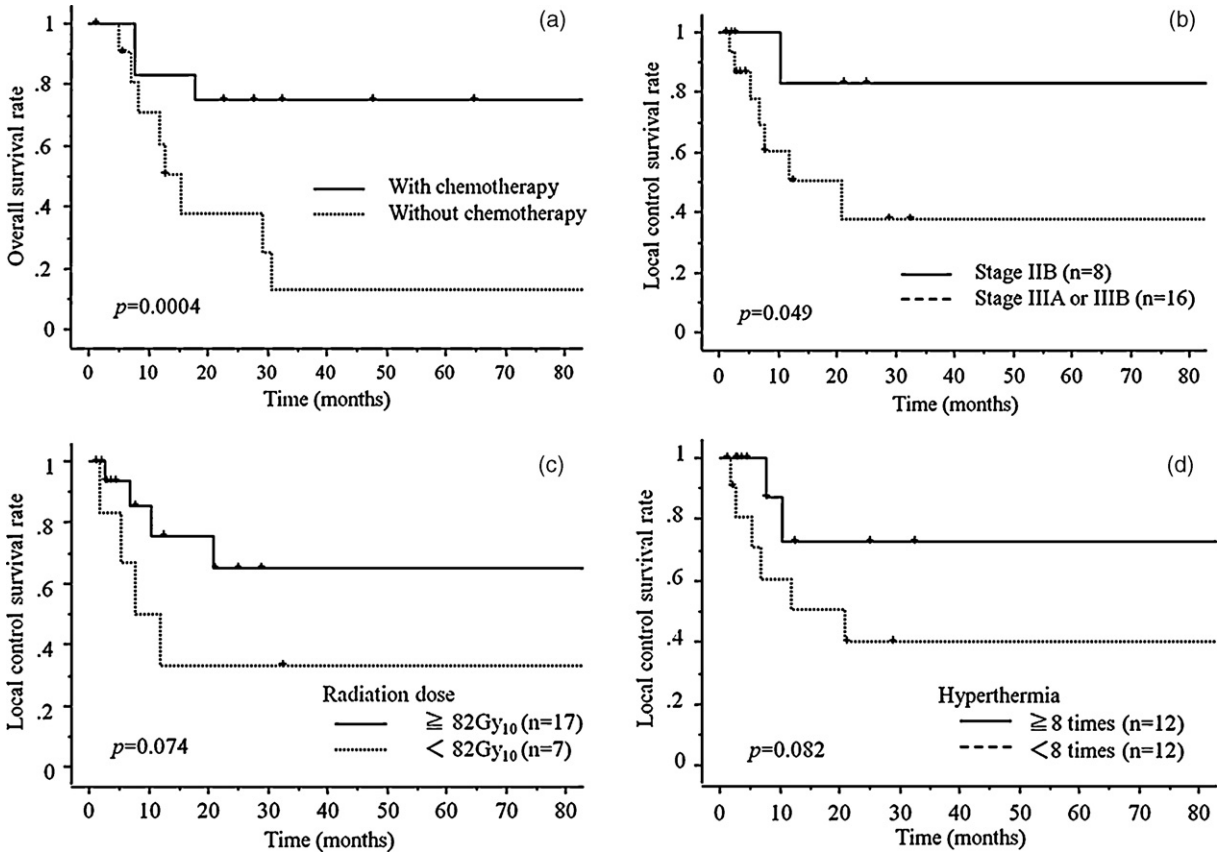

Fig. 2. (a) Chemotherapy was a significant predictor for overall survival rate ($p = 0.004$). (b) Clinical Stage (IIB) was a statistically significant prognostic indicator for local control survival rate ($p = 0.049$). (c) The use of a higher dose of RT ($\geq 82\,Gy_{10}$) tended to be a better prognostic indicator for local control ($p = 0.074$). (d) Trend toward significance was also seen between a higher number of hyperthermia treatments (≥ 8 times) and local control rate ($p = 0.082$).

Table 3
Univariate analysis of certain factors for survival rates.

Variable	*n*	Overall survival rate		Local control survival rate		Distant metastasis-free survival	
		3-Year (%)	*p*	3-Year (%)	*p*	3-Year (%)	*p*
Age							
≧65	12	14	0.033	48	0.852	33	0.046
<65	12	73		58		73	
PS							
0–1	14	59	0.170	73	0.217	70	0.325
2	10	30		33		24	
Pathology							
SqCC	8	50	0.435	70	0.561	44	0.345
Others	16	45		46		62	
Tumor size							
≧6cm	10	44	0.408	53	0.602	60	0.579
<6cm	14	50		55		51	
Stage							
IIB	8	75	0.153	83	0.049	67	0.941
IIIA–IIIB	16	33		38		50	
Total radiation dose (BED, Gy_{10})							
$\geq 82\,Gy_{10}$	17	48	0.338	65	0.074	66	0.243
$<82\,Gy_{10}$	7	42		33		28	
Hyperthermia							
≧8 times	12	50	0.998	73	0.082	57	0.742
<8 times	12	45		40		53	
Chemotherapy							
Yes	12	75	0.004	69	0.105	53	0.762
No	12	13		35		61	

BED, biologically effective dose; RT, radiotherapy.

41.7 °C. The $\%T \geqq 41$ °C ranged from 0 to 90%, with a median of 64%. No thermal parameters were significantly correlated with objective tumor response, overall and local control, and distant metastasis-free survival rates.

3.3. Acute and late toxicity

Acute toxicities ≥Grade 2 included acute dermatitis (Grade 3 in one patient; Grade 2 in two), and esophagitis (Grade 2 in one patient). Acute toxicities of Grades 4–5 were not observed. A skin burn that disappeared spontaneously after completion of combined therapy was observed in 2 patients. Late toxicity ≥Grade 2 was seen in 1 patient with radiation pneumonitis.

4. Discussion

The use of regional deep heating has been investigated, especially for the treatment of pelvic tumors and soft tissue sarcoma [10]. Randomized trials of RT with or without regional HT for cervical cancer demonstrate positive survival outcomes [25,26]. Scant information on the use of regional HT for the treatment of patients with lung cancer exists in the literature, probably because most available devices for regional deep heating are structurally difficult to apply to the thoracic region. However, some reports describe the feasibility and efficacy of regional HT using an 8-MHz RF-capacitive heating device with RT for patients with lung cancer [12–14,16]. Other than our prior reports, we know of only one other case series on clinical results of RT plus HT in patients with SSTs. Ebara et al. found that all but 1 of 5 patients with inoperable SST who received definitive RT plus regional HT with or without chemotherapy survived 3 years or more without recurrence [15].

The current study assessed clinical results for definitive RT plus regional HT with or without chemotherapy in 24 patients with SSTs. Regional HT-related toxicity in prior studies consisted of subcutaneous fat burns observed in 3–12% of patients. In general, these healed spontaneously and did not result in discontinuation of treatment [27,28]. Randomized phase III studies with deep regional HT do not show any increases in acute or late toxicity from RT [11]. Previous phase II trials of systemic chemotherapy with regional HT demonstrate that HT did not adversely influence the tolerability of the chemotherapeutic drugs, even when administered at maximum tolerated single modality doses [29]. In the current study, regional HT was well tolerated and did not reveal any significant increase in the toxicity from RT or chemotherapy.

Previous treatment results for SSTs are summarized in Table 4. Clinical outcomes with RT alone for SSTs are generally poor; however, many series have included patients with advanced stage tumors [5]. In general, 5-year survival rates for RT followed by surgery are approximately 30% [30]. The addition of chemotherapy to preoperative RT has improved clinical outcomes [3,4]. Our survival outcomes in patients with definitive RT plus regional HT with or without chemotherapy are promising compared with previous reports of definitive RT with or without chemotherapy (Table 4). In the present study, 88% of the patients with Stage IIB SSTs achieved local control. These data demonstrated our combined therapy to thus be a feasible alternative, especially in patients with unresectable SSTs, and the results justify further evaluations to definitively confirm the benefits of this therapeutic modality. These data suggest that our combined therapy may be a feasible alternative in patients with operable as well as unresectable disease.

Over the last two decades, combined chemotherapy with RT has been a subject of intense clinical research in locally advanced NSCLC. Data suggest that chemotherapy increases the efficacy of RT in locally advanced inoperable NSCLC, although the gain from the combined modality approach should be balanced against enhanced early toxicity [31]. In patients with locally advanced NSCLC, two recent randomized studies that compared concurrent vs. sequential chemoradiotherapy showed that the concurrent approach provided a superior outcome [32,33]. Hyperthermia has been shown to significantly enhance drug effectiveness [10,34]. For platinum drugs, enhancement takes place even at low temperatures without a threshold [34,35]. Various mechanisms may therefore account for the observed increased chemotherapeutic effects at elevated temperatures, e.g. an increased drug uptake into the cells, increased DNA damage, decreased DNA repair, reduced oxygen radical detoxification and increased membrane damage [34–36]. In our study, the use of chemotherapy improved the overall survival. We supposed that this chemotherapeutic regimen might mainly play a role in the improvement of the local control as a radiation-sensitizer, because the local control rate in the patients receiving this chemotherapy was slightly better ($p = 0.10$), and the distant metastasis-free survival was not observed to improve in those patients. However, this study was a retrospective case series without any specific chemotherapy protocol. Therefore, additional prospective clinical studies using chemoradiotherapy plus regional HT with detailed treatment protocols in patients with SSTs are strongly recommended.

Modern RT planning techniques allow a more conformal dose distribution around the tumor, potentially minimizing the RT dose to adjacent critical structures and permitting escalated dose delivery to the tumor [30]. A dose of 66 Gy improved survival in patients with SSTs who received definitive RT with sequential or concurrent chemotherapy [9]. In the present study, the use of a higher dose of RT tended to be a better prognostic indicator for local control based on univariate analyses; ≧Grade 3 complications were observed in only one patient, although a higher dose of RT was not a predictor for local control in multivariate analyses. A higher RT dose with regional HT should also be evaluated on further clinical studies in patients with SST.

Some reports of RT plus regional HT note that direct measurements of tumor temperature tend to correlate with lung cancer tumor response [12,13]. Numerous reports of superficial or pelvic tumors treated with RT plus HT also indicate a positive interrelationship between thermal and clinical parameters and effectiveness [10,37,38]. In the present study, trends toward significance were seen between a higher number of hyperthermia

Table 4
Previous study of either definitive radiotherapy or chemoradiotherapy without surgery for SST.

Study	Modality	*n*	Stage	RT (Gy)	Local control rate	5-Year overall survival rate
Komaki et al. [6]	RT	36	II: 2 III: 34	58 (40–64)	47%	23% (MST: 14 months)
Van Houtte et al. [7]	RT	31	–	20–70	55%	23%
Ahmad et al. [8]	RT	34	–	50–60	–	21%
Komaki et al. [9]	RT	45	IIB: 5 IIIA: 5 IIIB: 35	60 (16–70)	32%	9%
	CRT	32	IIB–IIIB	64 (19–70)	44%	36% (with ≧66 Gy)
Kappers et al. [18]	CRT	28	IIB–IIIB (inoperable)	66–88	68%	20%
Ebara et al. [15]	RHT or CRHT	5	IIIB	70 (68–70)	60%	–
Current study	RHT or CRHT	24	IIB: 8 IIIA: 2 IIIB: 14	70 (60–84)	55%	47% (MST: 30 months)

RT, radiotherapy; MST, median survival time; RHT, radiotherapy plus hyperthermia; CRHT, chemoradiotherapy plus hyperthermia.

treatments and local control rate. However, tumor temperature did not correlate with either the objective tumor response or survival rates, thus suggesting that the higher thermal dose is not necessary for multimodality therapy of SST. Experimental results have shown that lower thermal doses may mainly affect reoxygenation, whereas higher thermal doses may involve inhibition of DNA repair and direct cytotoxicity [39,40]. In addition, a clinical study of locally advanced breast carcinoma treated with chemoradiotherapy plus HT showed a paradoxical relation between the thermal dose and treatment response; tumor reoxygenation seemed to be temperature-dependent and associated with lower thermal doses [40]. Further experimental and clinical analyses to determine the relations between thermal dose, tumor oxygenation, and clinical outcome in multimodality therapy are needed. This study could not assess the additional value of HT to RT since a small number of patients in a single institution were retrospectively evaluated without a control group. Therefore, a phase II trial is needed to determine the efficacy for this combined therapy in patients with SSTs.

Regarding limitations associated with this study. Due to the fact that this study was a small retrospective case series with heterogeneous treatment, the possibility of some selection bias in regard to the prognostic factors could not be ruled out, although we did perform both univariate and multivariate analyses for the survival rates. A formal prospective trial is consequently needed to determine the efficacy and prognostic factors of this combined therapy in patients with SST.

In summary, the results of our study confirm that definitive RT plus regional HT, with or without chemotherapy, is a feasible and promising approach for treating SST. Use of chemotherapy may be effective in this combined therapy. Our outcomes justify further evaluation. Prospective clinical trials with detailed treatment protocols could assess the value of multimodal therapy consisting of definitive RT, regional HT, and chemotherapy in a larger number of patients with SST.

Conflict of interest

Potential conflicts of interest do not exist in this study.

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