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Original article

Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of the thoracic esophagus

Masakatsu Onozawa [a,*], Keiji Nihei [a], Satoshi Ishikura [c], Keiko Minashi [b], Tomonori Yano [b], Manabu Muto [b], Atsushi Ohtsu [b], Takashi Ogino [a]

[a] Radiation Oncology Division, National Cancer Center Hospital East, Chiba, Japan
[b] Gastrointestinal Oncology/Digestive Endoscopy Division, National Cancer Center Hospital East, Chiba, Japan
[c] Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

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ABSTRACT

Background and purpose: There are some reports indicating that prophylactic three-field lymph node dissection for esophageal cancer can lead to improved survival. But the benefit of ENI in CRT for thoracic esophageal cancer remains controversial. The purpose of the present study is to retrospectively evaluate the efficacy of elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for thoracic esophageal cancer.

Materials and methods: Patients with squamous cell carcinoma (SCC) of the thoracic esophagus newly diagnosed between February 1999 and April 2001 in our institution was recruited from our database. Definitive chemoradiotherapy consisted of two cycles of cisplatin/5FU repeated every 5 weeks, with concurrent radiation therapy of 60 Gy in 30 fractions. Up to 40 Gy radiation therapy was delivered to the cervical, periesophageal, mediastinal and perigastric lymph nodes as ENI.

Results: One hundred two patients were included in this analysis, and their characteristics were as follows: median age, 65 years; male/female, 85/17; T1/T2/T3/T4, 16/11/61/14; N0/N1, 48/54; M0/M1, 84/18. The median follow-up period for the surviving patients was 41 months. Sixty patients achieved complete response (CR). After achieving CR, only one (1.0%; 95% CI, 0–5.3%) patient experienced elective nodal failure without any other site of recurrence.

Conclusion: In CRT for esophageal SCC, ENI is effective for preventing regional nodal failure. Further evaluation of whether ENI leads to an improved overall survival is needed.

Surgery is the standard treatment for patients with resectable esophageal cancer. Radiation therapy alone has been indicated for unresectable or medically inoperable patients as a definitive or palliative treatment [1–3].

In the 1980s, some prospective studies showed encouraging results for chemoradiotherapy (CRT) of esophageal cancer [4,5]. The results of a phase III randomized trial comparing CRT with radiation alone (Radiation Therapy Oncology Group (RTOG) 85-01) have made CRT a standard treatment for patients who chose non-surgical definitive treatment for esophageal cancer [6–8]. During the last decade, most patients with newly diagnosed squamous cell carcinoma (SCC) of the esophagus were treated with definitive CRT in our institution.

Since the early 1980s, Japanese surgeons have practiced three-field regional lymph nodes dissection for esophageal cancer [9,10]. There are some reports indicating that prophylactic three-field lymph node dissection for esophageal cancer can lead to an improved survival [11,12]. In accordance with the concept of three-field lymph node dissection in curative surgery, ENI has been adopted for definitive CRT at our institution, but the benefit of ENI in CRT for thoracic esophageal cancer remains controversial [13–17]. The purpose of this study is to retrospectively evaluate the efficacy of ENI in CRT for thoracic esophageal cancer.

Methods and materials

Patient population

Patients newly diagnosed with SCC in the thoracic esophagus and treated with definitive CRT between February 1999 and April 2001 at our institution was recruited from our database on the basis of the following criteria: age ⩽75 years, adequate organ function, no other site of carcinoma except for early stage, and ENI treatment. Patients who could not complete the planned radiation therapy were excluded from this analysis. Informed consent was obtained from all patients.

* Corresponding author. Address: Radiation Oncology Division, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
E-mail address: maonozaw@east.ncc.go.jp (M. Onozawa).

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Pretreatment evaluation

Pretreatment evaluation included barium swallowing, endoscopy of the esophagus, and computed tomography (CT) of the neck, chest and abdomen. Lymph nodes were defined as metastatic if they were $\geqslant 1$ cm in their greatest diameter on CT imaging.

Clinical staging was diagnosed according to the UICC TNM Classification of Malignant Tumors 6th edition.

Treatment details

Treatment consisted of two cycles of CDDP 40 mg/m^2 on days 1 and 8 and continuous infusion of 5FU 400 mg/m^2/d on days 1–5 and 8–12, repeated every 5 weeks, with concurrent radiation therapy of 60 Gy in 30 fractions over 8 weeks, including a 2-week break. An additional two cycles of CDDP 80 mg/m^2 on day 1 and continuous infusion of 5FU 800 mg/m^2/d on days 1 to 5 every 4 weeks were administered for responders.

All patients underwent CT-based planning. Up to 40 Gy, radiation therapy was delivered to the primary tumor, metastatic lymph nodes, and regional nodes as ENI using anterior–posterior opposed fields. Regardless of the subsite of primary tumor, the lower cervical, periesophageal, mediastinal and perigastric, except celiac, nodes were included as regional lymph nodes. For the tumor of the upper thoracic esophagus, supraclavicular nodes were also included and for lower esophagus, celiac nodes were included. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes using bilateral oblique or multiple fields. The clinical target volume for the primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally. The planning target volumes for primary tumors, metastatic lymph nodes and regional nodes were determined with a 1–1.5 cm margin to compensate for set-up variations and internal organ motion. The treatment portal covered the planning target volume plus 0.5 cm margin to account for penumbra. Fig. 1 shows an example of a radiation field. Lung heterogeneity corrections were not used.

Follow-up evaluation

The following evaluations were performed until disease progression every 3 months for the first year and every 6 months thereafter: physical examination, endoscopy of the esophagus, CT scan of the neck, chest, and abdomen. Biopsy of the primary tumor site was routinely performed at each follow-up examination. After disease progression was defined, clinical evaluations were performed as required.

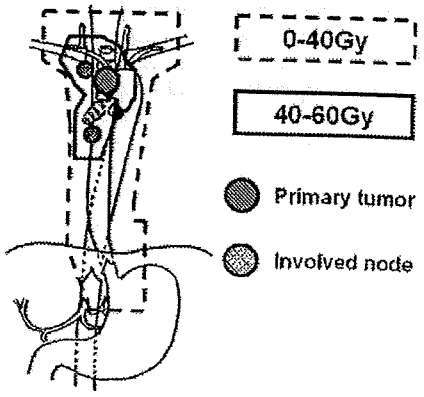

Fig. 1. An example of radiation field.

Response assessment

Complete response (CR) for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared with a negative biopsy.

Local control was defined as no detection of recurrent tumors in the same site from the time of CR until the last follow-up.

CR for metastatic lymph nodes was defined as the complete disappearance of all measurable and assessable disease for $\geqslant 4$ weeks. Uncertain CR was defined as the persistence of small nodes (<1 cm) with no evidence of progression at $\geqslant 3$ months after the completion of treatment, and patients with uncertain CR were grouped with those with CR for analysis.

Patterns of failure

Patterns of treatment failure were defined as the first site of failure. Local failure included the primary tumor. Involved node failure included the metastatic lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes. Elective nodal failure was defined as the recurrence of initially uninvolved lymph nodes within the ENI field.

Results

Patient characteristic

One hundred five patients received definitive CRT for esophageal cancer during the period examined. One hundred two patients matched the recruitment criteria, and three patients who could not complete the 60 Gy radiation therapy were excluded from the analysis. The reasons for stopping radiation therapy were (1) sever esophagitis at 56 Gy, (2) sepsis at 52 Gy, (3) disease progression at 48 Gy. The toxicities of remaining 102 patients were mild esophagitis and dermatitis. One hundred two patients characteristics are listed in Table 1. The median age was 64 years old, ranging from

Table 1
Patient characteristics.

Characteristic		Number of patients (n = 102)
Male/female		85/17
Age, years	Range	39–75
	Median	64
Histology	Squamous cell carcinoma	102
	others	0
Primary Site	Upper thoracic portion	14
	Mid-thoracic portion	50
	Lower thoracic portion	38
Tumor length, cm	Range	1–20
	Median	5
T	1	16
	2	11
	3	61
	4	14
N	0	48
	1	54
M	0	84
	1a	5
	1b	13
Stage	I	14
	IIA	28
	IIB	1
	III	41
	IVA	5
	IVB	13

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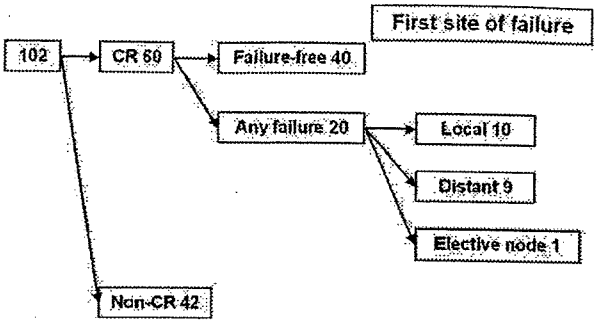

Fig. 2. The initial response after CRT and the patterns of failure.

39 to 75 years. The tumor histology was SCC in all patients. The subsites of the primary tumors were upper/middle/lower thoracic portions, 14/50/38; T1/T2/T3/T4, 16/11/61/14; N0/N1, 48/54; M0/M1a/M1b, 84/5/13; Stage I/II/III/IV, 14/29/41/18. The metastases sites of 11 M1b patients were lower cervical, supraclavicular or celiac lymph nodes.

The remaining two patients with tiny lung metastases were treated with definitive CRT at the physicians' discretion. After concurrent CRT, 69 patients who achieved CR or partial response received one or more additional cycles of chemotherapy.

Response, survival and patterns of failure

The initial response after CRT and the patterns of failure are shown in Fig. 2. The median follow-up durations for all patients and for surviving patients were 17 months (range 3–62 months) and 41 months (range 9–62 months), respectively. Fig. 3 shows overall survival data for all patients. Three-year overall survival rates were 43%. Sixty of 102 patients achieved CR (59%; 95% confidence interval [CI], 49% to 69%). After achieving CR, 40 patients never experienced any failure with a median follow-up period of 40 months (range 3 to 60 months).

In the remaining 20 patients, the first sites of failure were local (10 patients), distant (9 patients), and elective nodal failure (1 patient). The patient with elective nodal failure did not develop any other site of recurrence and died of pneumonia due to nodal failure.

Discussion

After an intergroup randomized controlled trial (RTOG 85-01) that compared definitive CRT with radiotherapy alone, the combined modality treatment became a standard therapy for patients who received non-surgical treatment for esophageal cancer. However, it was also reported that the persistence of loco-regional disease was the greatest cause of treatment failure, even in the CRT group in this trial [6–8]. In an attempt to improve local control, a dose escalation trial (Inter group study 0123) that compared the standard CRT dose (50.4 Gy/28 Fx) with a high dose (64.8 Gy/36 Fx) was conducted, but significant benefits of higher dose radiation therapy were not demonstrated [18–21]. As a result, the standard radiation dose is still 50.4 Gy/28 Fx for patients who receive 5FU/cisplatin-based combined modality therapy.

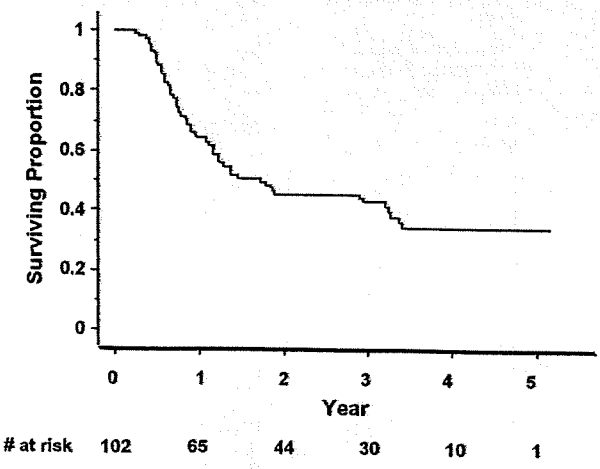

Fig. 3. The overall survival data for all patients.

Regarding the radiation field (target volume) of CRT for esophageal cancer, there is no global consensus for whether ENI should be performed or not. In the RTOG 85-01 trial, radiation was delivered at 30 Gy from the supraclavicular fossae to the esophagogastric junction as ENI, followed by cone down of 20 Gy to the primary tumor with 5 cm proximal and distal margins. On the other hand, in the INT0123 trial, ENI was omitted to improve the tolerance to treatment.

In our institution, ENI has been used because the results of most surgical series in Japan indicate a survival benefit of prophylactic three-field lymph node dissection for SCC in the thoracic esophagus [11,12]. Prophylactic three-field lymph node dissection has revealed occult regional lymph node metastasis, also known as micrometastases, found only through histopathology. It is thought that prophylactic three-field lymph node dissection improves the survival rate by eliminating micrometastases and reducing the regional lymph node recurrence rate.

In the current study, only one patient (1.0%; 95% CI, 0–5.3%) with elective nodal failure was identified without any failures of the other sites. This result suggests that if the gross tumor is controlled with CRT, ENI may prevent elective nodal failure. This preventive activity may occur through control of micromeastases.

However, it is not clear whether ENI improves overall survival. The incidence of local/regional failure and the persistence of disease in the CRT arm of RTOG 85-01, which used ENI, was lower than that in the standard dose arm of INT0123, which omitted ENI (46% vs. 55%), but the median survival times and the 2-year overall survival rates were similar in both groups (14.1 months, 36% vs. 18.1 months, 40%). On the other hand, there are concerns about the adverse effects of ENI. We previously reported long-term toxicity after definitive CRT for thoracic esophageal SCC [13]. Of 78 patients who achieved CR after CRT with the same regimen used in this study, 16 suffered from late cardiopulmonary toxicities and 8 were considered to die from toxicities related to CRT. Therefore, although ENI can reduce local/regional failures, substantial late toxicities may mitigate its survival benefits.

To minimize long-term toxicity without compromising the efficacy of CRT, we modified our radiation therapy technique for thoracic esophageal cancer in 2004. We adopted the same treatment regimen as the INT0123 trial by reducing the total dose from 60 to 50.4 Gy. The irradiation technique was also changed from conventional opposed fields to the multiple-field technique to avoid excessive dosing to the surrounding normal tissues. To maintain efficacy, we continued using ENI of 41.4 Gy in 23 fractions followed by 9 Gy in 5 fractions to the primary tumor and metastatic lymph nodes because our preliminary results suggested that ENI could control regional lymph node failure. We expect that the overall survival rate could be improved by reducing long-term toxicity.

References

[1] Okawa T, Kita M, Tanaka M, Ikeda M. Result of radiotherapy for inoperable locally advanced esophageal cancer. Int J Radiat Oncol Biol Phys 1989;17:49–54.

[2] Slevin NJ, Stout R. Carcinoma of oesophagus: a review of 108 cases treated by radical radiotherapy. Clin Radiol 1989;40:200–3.

[3] Hyden EC, Langholz B, Tilden T, et al. External beam and intraluminal radiotherapy in the treatment of carcinoma of the esophagus. J Thorac Cardiovasc Surg 1988;96:237–41.
[4] Coia LR. Chemoradiation as primary management of esophageal cancer. Semin Oncol 1994;21:483–92.
[5] Forastier AA, Orringer MB, Perez-Tamayo C, Urba SG, Zahurak M. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. J Clin Oncol 1993;11:1118–23.
[6] Herskovic A, Martz K, Al-Sarraf M, et al. Combined chemotherapy and radiotherapy in patients with cancer of esophagus. N Engl J Med 1992;326:1593–8.
[7] Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 1997;15:277–84.
[8] Cooper J, Guo M, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow up of prospective randomized trial (RTOG 85-01). JAMA 1999;281:1623–7.
[9] Bumm R, Wong J. More or less surgery for esophageal cancer: extent of lymphadenectomy for squamous cell esophageal carcinoma – how much is necessary? Dis Esophagus 1994;7:151–5.
[10] Japanese Society for Esophageal Disease. Clinicopathological aspects. In: Guidelines for clinical and pathologic studies on carcinoma of the esophagus. 9th ed. Tokyo: Kanehara & Co., Ltd.; 1999. p. 1–34.
[11] Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–73.
[12] Kato H, Watanabe H, Tachimori Y, Iizuka T. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann Thorac Surg 1991;51:931–5.
[13] Ishikura S, Nihei K, Ohtsu A, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003;21:2697–702.
[14] Ohtsu A, Boku N, Muro K, et al. Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of esophagus. J Clin Oncol 1999;17:2915–21.
[15] Hironaka S, Ohtsu A, Boku N, et al. Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with $T_{2\text{-}3}N_{any}M_0$ squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 2003;57:425–33.
[16] Sugaya S, Ohara K, Okumura T, Irie T, Nakajima K, Itai Y. Pattern of initial treatment failure of esophageal cancer following radiotherapy. Nippon Acta Radiol 1999;59:754–9.
[17] Yorozu A, Dokiya T, Suzuki T, Toya K. Elective regional nodal irradiation for esophageal carcinoma. Jpn J Cancer Clin 2000;46:244–6.
[18] Minsky BD, Neuberg D, Kelsen DP, et al. Final report of intergroup trial 0122 (ECOG PE-289, RTOG 90-12): phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high dose radiation for squamous cell carcinoma of esophagus. Int J Radiat Oncol Biol Phys 1999;43:517–23.
[19] Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg R, Benson 3rd A. Neoadjuvant chemotherapy plus concurrent chemotherapy and high dose radiation for squamous cell carcinoma of esophagus: a preliminary analysis of the phase II intergroup trial 0122. J Clin Oncol 1996; 14:149–55.
[20] Minsky BD, Berkey B, Kelsen D, et al. Preliminary results of Intergroup INT0123 randomized trial of combined modality therapy (CMT) for esophageal cancer: standard VS high dose radiation therapy. Proc Am Soc Clin Oncol 2000;19:239a [abstr. 927].
[21] Minsky BD, Pajak TF, Ginsberg RJ, et al. INT0123 (Radiation therapy oncology group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 2002;20:1167–74.

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Original Article

Superselective High-Dose Cisplatin Infusion With Concomitant Radiotherapy in Patients With Advanced Cancer of the Nasal Cavity and Paranasal Sinuses

A Single Institution Experience

Akihiro Homma, MD, PhD[1]; Nobuhiko Oridate, MD, PhD[1]; Fumiyuki Suzuki, MD, PhD[1]; Shigenari Taki, MD[1]; Takeshi Asano, MD[2]; Daisuke Yoshida, MD[2]; Rikiya Onimaru, MD, PhD[2]; Takeshi Nishioka, MD, PhD[2]; Hiroki Shirato, MD, PhD[2]; and Satoshi Fukuda, MD, PhD[1]

BACKGROUND: The current study aimed to evaluate the efficacy of superselective high-dose cisplatin infusion with concomitant radiotherapy (RADPLAT) for previously untreated patients with advanced cancer of the nasal cavity and paranasal sinuses. **METHODS:** Between October 1999 and December 2006, 47 patients were given superselective intra-arterial infusions of cisplatin (100-120 mg/m^2 per week) with simultaneous intravenous infusions of thiosulfate to neutralize cisplatin toxicity and conventional external-beam radiotherapy (65-70 grays). **RESULTS:** There were 7 patients (14.9%) diagnosed with T3, 22 (46.8%) with T4a, and 18 (38.3%) with T4b disease. During the median follow-up period of 4.6 years, the 5-year local progression-free survival rate was 78.4% for all patients (n = 47), 69.0% for patients with T4b disease (n = 18), and 83.2% for patients with <T4b disease (n = 29). The 5-year overall survival rate was 69.3% for all patients, 61.1% for patients with T4b disease, and 71.1% for patients with < T4b disease. RADPLAT was feasible in 45 patients (95.7%). No patient died as a result of treatment toxicity or had a cerebrovascular accident. Osteonecrosis (n = 7), brain necrosis (n = 2), and ocular/visual problems (n = 16) were observed as late adverse reactions. **CONCLUSIONS:** Although a single institution experience, the results of the current study suggest that RADPLAT can cure the majority of patients with advanced cancer of the nasal cavity and paranasal sinuses, as well as preserve organs. Late adverse reactions should be monitored in future studies. Cancer 2009;115:4705–14. © 2009 American Cancer Society.

KEY WORDS: intra-arterial, cisplatin, organ preservation, chemoradiotherapy.

Corresponding author: Akihiro Homma, MD, PhD, Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan; Fax: (011) 81-11-717-7566; ak-homma@med.hokudai.ac.jp.

[1]Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan; [2]Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

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Malignancies of the nasal cavity and paranasal sinuses are rare neoplasms that account for only 3% of head and neck carcinomas and approximately 0.5% of all malignant diseases.[1] However, it is more frequently observed in Japan, with 7% of all cancers arising in the upper aerodigestive tract.[2]

Because of the anatomic limitations in making an early diagnosis and the absence of symptoms in early stage disease, a large population of these lesions are advanced at the time of initial presentation. Most advanced cases require radical surgery followed by postoperative radiation. Frequently, this amounts to a total maxillectomy or a craniofacial resection with or without a complete obliteration of the contents of the orbit. These surgeries result in significant disfigurement and impairment of function. Despite such radical therapy, the oncologic outcomes of survival and disease control are not satisfactory.

For these reasons, many patients refuse surgery, instead opting for less conventional treatments with lower cure rates in an effort to spare themselves potential surgical morbidity. Because radiotherapy alone is considered ineffectual for advanced, unresectable head and neck cancers,[3,4] there has been great interest in combined radiotherapy and chemotherapy. Prospective randomized trials have demonstrated improved survival rates in patients treated with chemoradiotherapy (CRT) compared with radiotherapy alone for unresectable squamous cell carcinoma (SCC) of the head and neck.[5-7]

It has also been shown that concurrent radiotherapy and targeted chemotherapy with cisplatin (hereafter referred to as RADPLAT) is a promising treatment,[8,9] achieving a 90% complete response rate in patients with advanced head and neck cancer.[10] The treatment program incorporates a novel technique for infusing cisplatin directly into the tumor bed, while minimizing the effects of the drug systemically.

Although trials using RADPLAT in patients with cancer of the nasal cavity and paranasal sinuses have been performed at several institutions recently, RADPLAT has mainly been used as a preoperative treatment,[11,12] with to our knowledge only a few studies testing it as a definitive treatment.[13] Herein, we used RADPLAT for the definitive treatment of patients with cancer of the nasal cavity and paranasal sinus, and analyzed and discussed the outcomes.

MATERIALS AND METHODS

Eligibility Criteria

Eligible patients were aged ≤75 years and had to have a World Health Organization performance status of 0 to 2, adequate bone marrow reserve, and adequate liver and renal function. Written informed consent was obtained from all patients before entry into the study. Patients who were pregnant or breastfeeding were excluded from the study. Patients also were required to have histologic proof of carcinoma of the nasal cavity or the paranasal sinuses classified as T3 to T4 disease. All patients were initially evaluated by a multidisciplinary team comprised of head and neck surgeons and radiation oncologists, and tumors were classified according to the 2002 International Union Against Cancer staging system. The stage of the tumor was determined on the basis of patient history, physical examination, and chest x-rays, as well as computed tomography (CT), magnetic resonance imaging (MRI), or both. Patients either had disease for which radical surgery was contraindicated or had rejected radical surgery.

Patients with a pathologic diagnosis of SCC, undifferentiated carcinoma, and adenoid cystic carcinoma were eligible for the study, but not if they had distant metastases (M1) or had received prior treatment of any kind for their cancer.

Chemotherapy

All patients received concurrent intra-arterial (IA) cisplatin and intravenous sodium thiosulfate infusions in the following manner: cisplatin (at a dose of 100-120 mg/m^2 per week for 4 weeks) was infused through a microcatheter that was placed angiographically to selectively encompass only the dominant blood supply of the targeted tumor. Tumors of the nasal cavity or paranasal sinuses are usually covered by the internal maxillary artery, but in cases in which the facial artery, transverse facial artery, or ascending pharyngeal artery covered the tumor, part of the dose was administered through these alternative arteries.

First, the catheter was positioned in the region of expected blood supply. Contrast agent was then injected as rapidly as possible until it refluxed slightly into the more proximal vessels during peak systole. Next, selective IA CT arteriography (IA-CTA) was performed to correctly and carefully identify the feeding arteries and their perfusion,

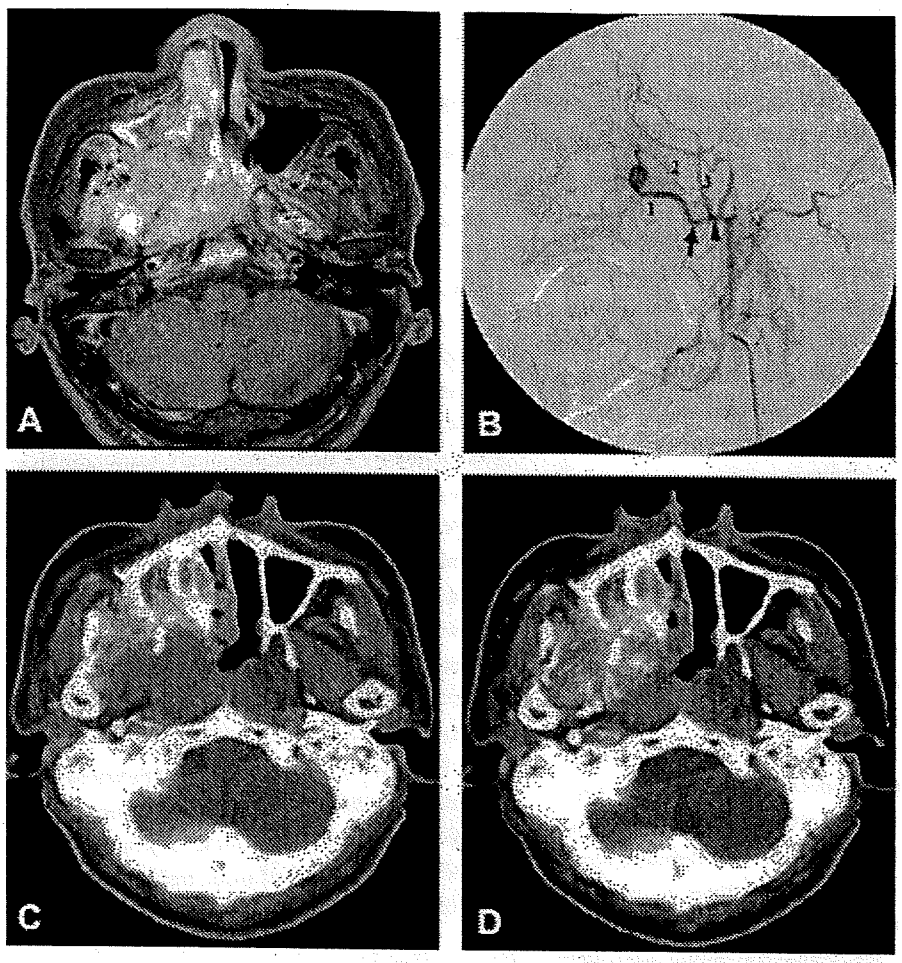

FIGURE 1. (A) Findings from a 57-year-old man with a right maxillary sinus cancer that was classified as T4bN2bM0 are shown. (B) A lateral subtraction angiogram of right external carotid artery is shown. The internal maxillary artery (indicated by 1), accessory meningeal artery (indicated by 2), and middle meningeal artery (indicated by 3) are shown. (C) Intra-arterial computed tomographic arteriography (IA-CTA) was performed after a microcatheter was placed just beyond the middle meningial artery (arrow in Fig. 1B). The IA-CTA demonstrated a tumor with enhancement in the anterior but not posterior portion. (D) The catheter was then placed just in front of the middle meningial artery (arrowhead in Fig. 1B). IA-CTA indicated that the majority of the tumor was enhanced at this time. The posterior portion of the tumor was considered to be covered by the accessory meningial artery.

and cisplatin was infused at the determined rate (Figs. 1 and 2). Simultaneously, sodium thiosulfate (at a dose of 20-24 g) was given intravenously, as described by Robbins et al, to neutralize the cisplatin.[10] All arterial catheterizations were accomplished transcutaneously through the femoral artery, and the catheters were removed immediately after infusion. So that patients excreted the cisplatin rapidly, 8 L of lactated Ringer solution were given over a 24-hour period. A 5HT3-receptor antagonist was given to all patients before arterial infusion to minimize nausea and vomiting. Chemotherapy was completed during the first 4 weeks, provided that patients responded well in the early treatment period and had received 3 arterial infusions.

Radiotherapy

All patients received external radiotherapy using a 4-megavolt (MV) or 6-MV x-ray linear accelerator. The irradiation treatment volume included the entire maxilla, ethmoid sinus, ipsilateral nasal cavity, and

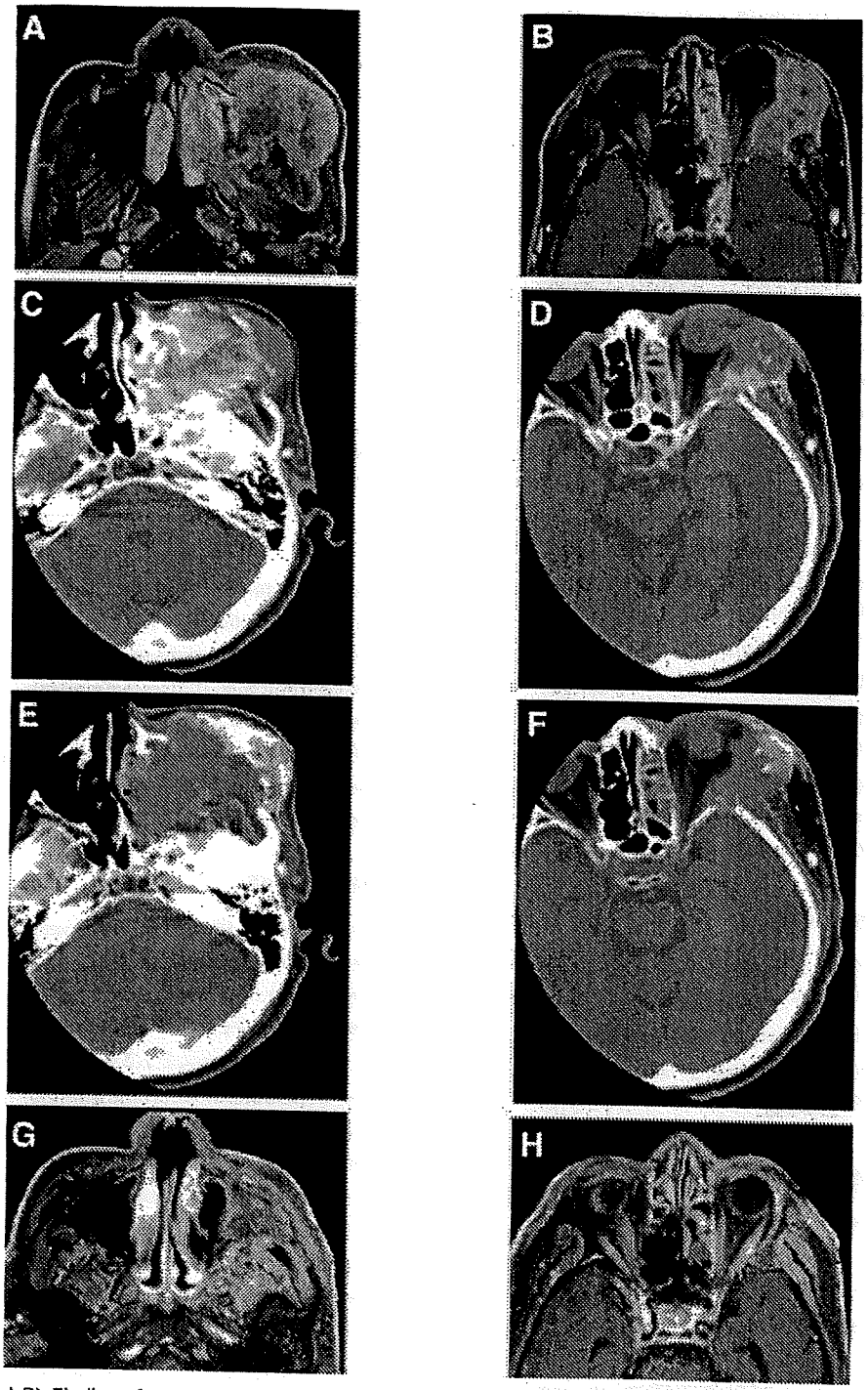

FIGURE 2. (A and B) Findings from a 70-year-old man with a left maxillary sinus cancer classified as T4bN0M0 are shown. (C and D) Tumor enhancement was identified with intra-arterial computed tomographic arteriography (IA-CTA) of the internal maxillary artery. The facial tissue that was anterior and lateral of the maxillary sinus was not found to be enhanced. (E and F) IA-CTA of the transverse facial artery confirmed that this area was enhanced by the transverse facial artery. (G and H) Magnetic resonance imaging scans indicated the disappearance of the tumor 5 months after the completion of therapy. Tissue noted in the maxillary sinus was considered to be scar tissue. The patient was alive without disease after 30 months of follow-up.

pterygopalatine fossa. For patients with tumor extensions to the orbit, this area was also treated, but efforts were made to spare the lacrimal gland. The irradiation schedule was 65 grays (Gy) in 26 fractions over 6.5 weeks by May 2006. Since then, it has changed to 70 Gy in 35 fractions over 7 weeks for all patients with advanced head and neck cancer. The treatment volume was reduced to 40 Gy for patients in which there was a low possibility of tumor extension to adjacent structures such as the ethmoid sinus or orbit.

A modified 45-wedged pair technique was used, in which the lateral beams were tilted approximately 10 degrees anteriorly with a hope of reducing the risk of temporal lobe necrosis. Multileaf collimators were also used for this purpose and to reduce the dose to other critical structures, such as the optic chiasm and contralateral eye. For patients with lymph node metastases, the ipsilateral neck was irradiated (40 Gy) using an anteroposterior field and a 25 to 30 Gy boost was given to the positive lymph nodes. A thermoplastic mask was used for immobilization for all patients. CT and MRI scans were taken in the same position using the mask so that accurate diagnosis of the extent of the tumor could be made. The treatment was planned with a CT simulator and a 3-dimensional dose calculation computer. The dose to the spinal cord was kept below 40 Gy in all instances.

Management of the Neck

Patients with regional lymph node metastasis of the neck were treated with 65 to 70 Gy of radiotherapy and chemotherapy. If lymph node metastases remained or recurred, patients with resectable neck disease were referred for cervical lymph node dissection.

Evaluation of Response and Toxicity

Responses were evaluated by clinical examination and/or CT or MRI studies 6 to 8 weeks after the completion of therapy. Standard criteria were used to assess the patient response. A complete response was defined as total resolution of the macroscopically visible tumor, and a partial response was defined as a $\geq$50% reduction in the macroscopically visible tumor. Because it is difficult to differentiate between radiographic changes related to the treatment and scar tissue from persisting tumors, we labeled patient outcomes to reflect this uncertainty. Over time, scar tissue remains stable, but persistent tumor tissue will progress, so a patient with radiologic changes that remained stable and with no signs or symptoms of disease was considered to be free of disease progression. A biopsy was performed only to document disease recurrence, if indicated. All toxicities encountered during therapy were evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

Table 1. Patient Characteristics (n=47)

Characteristics	No. of Patients
Age, y	
Range	25-73
Median	56
Mean	56.3
Sex	
Male	36 (76.6%)
Female	11 (23.4%)
Primary tumor site	
Maxillary sinus	36 (76.6%)
Ethmoid sinus	8 (17.0%)
Nasal cavity	3 (6.4%)
Histology	
Squamous cell	36 (76.6%)
Undifferentiated	9 (19.1%)
Adenoid cystic	2 (4.3%)

Statistical Analysis

The major endpoint of the study was overall survival. Additional endpoints included local control rate (local progression-free rate) and toxicity. All patients were closely observed during the follow-up period, the median of which was 4.6 years (range, 2.1-9.2 years).

Cases of persistent or recurrent primary or neck disease after the completion of RADPLAT were considered to be local or regional failures, regardless of whether salvage therapy was successful. Probabilities of overall survival, which included death from any cause, and local control rates (local progression-free rates computed from the beginning of treatment to the time of local disease recurrence) were calculated by the Kaplan-Meier method.

RESULTS

Patient Characteristics

A total of 47 patients were entered in this study from October 1999 to December 2006 and were treated by

Table 2. T and N Classification (n = 47)

	No. of Patients by N Classification					
T Classification	0	1	2a	2b	2c	Total
3	6	1				7
4a	22	0				22
4b	13	1		2	2	18
Total	41	2		2	2	47

RADPLAT at Hokkaido University Hospital (Sapporo, Japan). There were 36 men and 11 women, with a median age of 56 years (range, 25-73 years). Detailed patient characteristics are listed in Table 1. Of the 47 patients, 36 (76.6%) had tumors arising in the maxillary sinus, 8 (17%) in the ethmoid sinus, and 3 (6.4%) in the nasal cavity. There were 36 patients (76.6%) who had SCCs, 9 (19.1%) undifferentiated carcinomas, and the remaining 2 (4.3%) had adenoid cystic carcinomas.

T and N classifications are shown in Table 2. There were 7 patients (14.9%) diagnosed with T3 disease, 22 (46.8%) with T4a disease, and 18 (38.3%) with T4b disease. Lymph node involvement was present in 6 patients (12.8%). Two patients with large tumors received induction chemotherapy before radiotherapy to avoid exposing the eyeball and/or optic nerve of the unaffected side to radiation. The protocol of induction chemotherapy was a combination of cisplatin, 5-fluorouracil, and docetaxel. One patient received 1 course and the other received 2 courses of treatment. Intensity-modulated radiotherapy was used for 1 patient to avoid exposing the eyeball and the optic nerve of the unaffected side to radiation.

Compliance

RADPLAT was feasible (3 or 4 infusions of IA cisplatin and a full dose of radiotherapy within 7 days of treatment interruptions) in 45 patients (95.7%). One patient received only 1 cycle of IA chemotherapy and had his radiotherapy interrupted for 30 days because of sepsis and poor general condition. Another patient experienced severe drug eruption after each IA chemotherapy, and therfore RADPLAT was withdrawn after 2 courses of IA chemotherapy and 50 Gy of radiotherapy. The patient then underwent a total maxillectomy.

Table 3. Acute Toxicity (n = 47)*

	No. of Patients by Toxicity Grade			
Toxicity	1	2	3	4
Allergic reaction		1		
Hearing	10	4		
Anemia	15	20	4	
Leukopenia	3	18	12	2
Thrombocytopenia	7	6	2	1
Arrhythmia	1			
Fever	13	6	5	
Alopecia	7	13		
Dermatitis	7	17		2
Nausea/vomiting	11	14	2	
Mucositis	4	19	9	
Diarrhea		1		
Liver dysfunction	10	3		
Neuropathy			1	1
Renal	1	2		

*All toxicities encountered during therapy were evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

Toxicity

Although the treatment regimen was intensive, acute toxicity was manageable in most patients (Table 3) and none died as a result of treatment toxicity. Thirty-five patients (74.5%) experienced grade 3 to 4 toxicity. Nonhematologic side effects included mucositis (n = 9), nausea/vomiting (n = 4), and neurologic signs (n = 2). No patient had a cerebrovascular accident. Hematologic toxicity consisted of leukopenia (n = 14), anemia (n = 4), and thrombocytopenia (n = 2). Arterial infusion had to be stopped after only 1 infusion in 1 patient who developed sepsis because of toxicity. No surviving patients required feeding tube support.

Osteonecrosis, brain necrosis, and ocular/visual problems occurred as late adverse reactions. A total of 7 patients experienced osteonecrosis, including 5 cases of the maxilla, 1 of the mandible, and 1 of the frontal bone. Patients with grade 3 mandible necrosis required reconstruction of the mandible with free flap transfer. The remaining 6 patients developed grade 2 osteonecrosis, which was manageable with minor sequestrectomy. Two patients developed brain necrosis. Of these, 1 developed seizures that were well controlled by an anticonvulsant drug. The other suffered mild dementia.

Severe ocular/visual problems (grade 3 of 4) occurred in 16 of the 38 patients who were followed over 2 years. One of these required enucleation of a painful eye ball. Severe ocular/visual problems occurred in 14

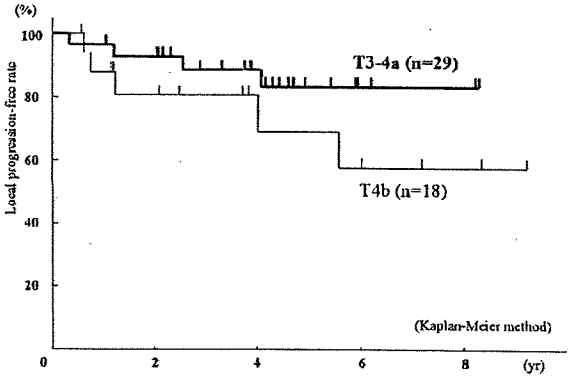

FIGURE 3. Local progression-free survival rate according to T classification is shown in 47 patients with cancer of the nasal cavity and paranasal sinuses.

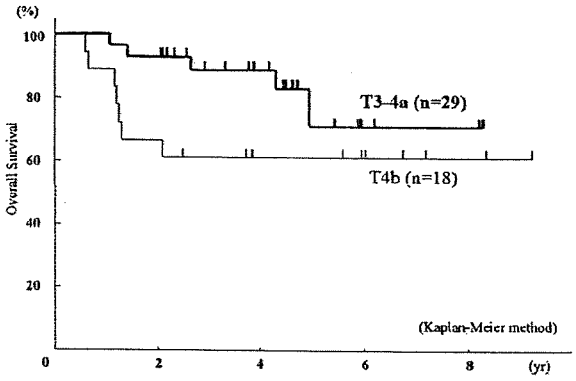

FIGURE 4. Overall survival according to T classification is shown in 47 patients with cancer of the nasal cavity and paranasal sinuses.

(56%) of 25 patients with tumors invading the orbit and/or invading the inferior wall of the orbit. These patients were considered for orbital exenteration if the need for radical surgery was indicated. Conversely, severe ocular/visual problems occurred in 2 (15.4%) of 13 patients without tumors invading the orbit and/or invading the inferior wall of the orbit.

Local Control and Overall Survival

The patient who experienced a severe drug eruption and underwent a total maxillectomy was treated as a local failure. The 5-year local progression-free survival rate was 78.4% for all patients (n = 47), 69.0% for patients with T4b disease (n = 18), and 83.2% for patients with < T4b disease (n = 29) (Fig. 3). The 5-year overall survival rate was 69.3 for all patients, 61.1% for patients with T4b disease, and 71.1% for patients with < T4b disease (Fig. 4).

Response of the Primary Disease

Of the 47 patients entered into the treatment program, complete responses in the primary site were obtained in 13 (27.7%) patients and partial responses in 31 (66.0%) patients. However, the primary disease was well controlled by RADPLAT in 39 patients (83.0%) at the time of last follow-up. The remaining 8 patients (17.0%) had persistent or recurrent primary disease after the completion of RADPLAT. Viable tumor cells were observed in a surgical specimen from the patient who underwent a total maxillectomy. Since then, the patient has had no further evidence of disease. He was included in the category of primary disease not controlled by RADPLAT.

Response of Neck Disease

Among the 6 patients with positive neck disease, 4 were well controlled by RADPLAT without surgery. One patient underwent a cervical lymph node dissection 4 months after treatment for a suspicious residual lymph node. Another patient had a lymph node that recurred 10 months after therapy, and therefore underwent a cervical lymph node dissection 11 months after the treatment. As a result, viable tumors were observed in the surgical specimens of both patients. Six patients classified as having N0 disease before therapy developed neck metastases after RADPLAT; of these, 4 were treated successfully by salvage neck dissection.

In 1 patient, neck disease and distant metastasis developed at the same time, whereas in another patient, the site of the primary tumor recurrence was found at the same time as neck disease. Neither patient was able to undergo a cervical lymph node dissection and therefore both were treated with systemic chemotherapy.

Pattern of Recurrence

The site of first disease recurrence was identified whenever possible. Recurrence first occurred at the primary tumor site in 8 patients. Of these, 3 underwent salvage surgery, but only 1 patient was successfully salvaged. Neck disease and distant metastasis were found at the same time in 2 patients, and distant metastasis was found in 3 patients without a primary or neck recurrence. Two patients died of other causes without evidence of disease.

DISCUSSION

Historically, sinonasal malignancies have been treated with primary radiotherapy. However, treatment with radiotherapy alone has produced disappointing results in the case of patients with primary advanced tumors.[14-16] In addition, high doses of radiation pose a significant risk for injury to optic structures, such as the retina, optic nerves, and chiasm.[17] Combined radical surgery and radiotherapy constitutes the standard treatment for patients with cancer of the nasal cavity and paranasal sinus as well as most epithelial malignancies.[18,19] However, the overall treatment of sinonasal malignancies has resulted in 5-year survival rates in the range of 30% to 50%, despite refinements in imaging studies such as CT scans and MRI, surgical techniques, and radiotherapy.[19-23] Moreover, survival is further reduced for patients with T4 tumors.

Functional and cosmetic outcomes after surgical treatment for advanced tumors, especially those classified as T4, are also far from satisfactory from the standpoint of patients. Therefore, some patients refuse surgical treatment, whereas others have unresectable disease. For these patients, radiotherapy is suggested, but is not expected to eliminate the tumor.[24]

Recently, prospective randomized trials have demonstrated improved survival rates in patients treated with CRT versus radiotherapy alone for unresectable SCC of the head and neck.[5-7] Harrison et al[25] also reported local progression-free survival rate of 94% among 20 patients with unresectable malignant tumors of the skull base who were treated with aggressive CRT, among whom were 15 patients with SCC. These findings indicate that CRT is the only viable option, and can be very effective in such cases of brain invasion by SCC.

Rosen et al achieved a long-term disease-free interval in 11 of 12 patients with paranasal sinus cancer (92% survival after a median follow-up of 55 months; range, 13-105 months) using multimodality therapy comprised of 5-fluorouracil–cisplatin-based neoadjuvant chemotherapy followed by standard surgical resection and radiotherapy with or without concomitant hydroxyurea and 5-fluorouracil.[26] These data represent encouraging numbers from a small series and suggest that chemotherapy has a role in the treatment of patients with paranasal sinus cancer.

Robbins, a pioneer of superselective arterial infusion of cisplatin, reported 5-year overall survival and locoregional control rates of 38.8% and 74.3%, respectively, in 213 patients with stage III to IV SCC of the head and neck.[8] IA delivery of chemotherapy has the potential to increase drug concentrations at tumor sites, whereas the IA infusion of cisplatin together with sodium thiosulfate enables the lowering of systemic toxicity. Paranasal sinus carcinomas tend to be encompassed mostly within the territory of terminal branches of the internal maxillary artery, which can be catheterized consistently and repeatedly; therefore, patients with such malignancies are good candidates for RADPLAT treatment.

A phase 2 protocol designed by the University of Tennessee Health Sciences Center in Memphis in 1993 takes advantage of the benefits of multimodality therapy.[11] Patients receive up to 4 weekly infusions of high-dose cisplatin by means of superselective transfemoral catheterization of the internal maxillary artery. Concurrently, they also receive 50 Gy of external-beam radiotherapy over 5 weeks. Definite surgical resection is performed 6 to 8 weeks after the completion of CRT. Results from the first 19 patients were recently reported within a median follow-up of 53 months. Of these, 16 patients (84%) had T4 disease. Surgery was conservative, with a high rate of preservation of orbital contents, visual function, midface structures, and palate, as well as a lack of any facial incisions, resulting in an improved overall cosmetic and functional outcome. The overall survival rates at 2 and 5 years were 67% and 51%, respectively. In the 13 patients in whom the disease was controlled after surgery, only 2 (15%) developed local failure. They reported no visual loss except for cataracts in 2 patients. However, 50 Gy of radiation is not enough to eradicate advanced cancer, even if surgery is combined. Conversely, delivering a high curative dose of radiation has been considered to result in damage to the optic nerve, chiasm, or brain.[17] We are concerned that reducing the radiation dose results in poor local control, because to our knowledge wide resection and postoperative radiotherapy have not previously been reported to achieve satisfactory survival rates.[19-23]

In our institution, RADPLAT is the definitive treatment of choice for patients with advanced nasal cavity and nasal paranasal sinus cancer to achieve improved survival rates and to avoid major surgery. We consider that patients with tumors invading orbital fat, orbital musculature, or involvement of the orbital apex usually require orbital content extirpation if surgery is indicated.[27] Therefore, we believe that eye-related complications may

occur in such patients, although efforts should be made to spare vision and to avoid complications using treatments such as intensity-modulated radiotherapy and heavy particle radiotherapy. Although some complications occurred in the current study, careful planning of radiation and IA infusion limited these to an acceptable level.

Although IA chemotherapy is sometimes regarded as dangerous because of the risk of catheter-related problems, cerebrovascular accidents, and severe systemic complications,[28,29] no treatment-related deaths were encountered in the current study and no cerebrovascular accidents occurred; indeed only 1 case of greater than 200 has occurred in our institution to date, with a full recovery reported. We consider this to be the result of careful patient selection, superselective catheterization, and the management of side effects and toxicities during RADPLAT therapy. Thus, the findings of the current study were of a better outcome than previous reports from many centers, and excellent cosmetic outcomes were achieved because surgery was not performed. Because patient numbers were small and this was a single-institution experience, a multi-institutional trial is needed to prove that this strategy is feasible and effective.

In conclusion, superselective high-dose cisplatin infusion with concomitant radiotherapy can result in organ preservation and cure in the majority of patients with advanced cancer of the nasal cavity and paranasal sinuses. Toxicity was manageable in the current study, and no patient died as a result of treatment toxicity. However, late adverse reactions such as osteonecrosis, brain necrosis, and ocular/visual problems should be monitored in future trials. Nonetheless, these results do suggest that significant progress has been made in the management of these diseases.

Conflict of Interest Disclosures

The authors made no disclosures.

References

1. Muir CS, Nectoux J. Descriptive epidemiology of malignant neoplasms of nose, nasal cavities, middle ear and accessory sinuses. *Clin Otolaryngol.* 1980;5:195-211.
2. Report of Head and Neck Cancer of Japan Clinical Statistics of Registered Patients, 2001. Japan Society for Head and Neck Cancer Registry Committee. *Jpn J Head Neck Cancer.* 2005;31(suppl): 92-110.
3. Marcial VA. Ninth annual del Regato lecture: optimal multidisciplinary management of head and neck cancer. *Int J Radiat Oncol Biol Phys.* 1987;13:393-401.
4. Glick JH, Taylor SG IV. Integration of chemotherapy into a combined modality treatment plan for head and neck cancer: a review. *Int J Radiat Oncol Biol Phys.* 1981;7:229-242.
5. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst.* 1994;86:265-272.
6. Merlano M, Benasso M, Corvo R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst.* 1996;88:583-589.
7. Al-Sarraf M, Pajak TF, Marcial VA, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG Study. *Cancer.* 1987;59:259-265.
8. Robbins KT. The evolving role of combined modality therapy in head and neck cancer. *Arch Otolaryngol Head Neck Surg.* 2000;126:265-269.
9. Homma A, Furuta Y, Suzuki F, et al. Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for advanced head and neck cancer. *Head Neck.* 2005;27: 65-71.
10. Robbins KT, Kumar P, Wong FS, et al. Targeted chemoradiation for advanced head and neck cancer: analysis of 213 patients. *Head Neck.* 2000;22:687-693.
11. Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg.* 2004;130:948-955.
12. Fujishiro Y, Nakao K, Watanabe K, et al. A new aspect of tri-modal therapy with superselective intra-arterial chemotherapy in maxillary sinus carcinoma. *Acta Otolaryngol Suppl.* 2007;(559):151-156.
13. Shiga K, Yokoyama J, Hashimoto S, et al. Combined therapy after superselective arterial cisplatin infusion to treat maxillary squamous cell carcinoma. *Otolaryngol Head Neck Surg.* 2007;136:1003-1009.
14. Isaacs JH Jr, Mooney S, Mendenhall WM, Parsons JT. Cancer of the maxillary sinus treated with surgery and/or radiation therapy. *Am Surg.* 1990;56:327-330.
15. Waldron JN, O'Sullivan B, Warde P, et al. Ethmoid sinus cancer: twenty-nine cases managed with primary radiation therapy. *Int J Radiat Oncol Biol Phys.* 1998;41:361-369.
16. Waldron JN, O'Sullivan B, Gullane P, et al. Carcinoma of the maxillary antrum: a retrospective analysis of 110 cases. *Radiother Oncol.* 2000;57:167-173.
17. Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. *Int J Radiat Oncol Biol Phys.* 1988;14:11-22.

18. Katz TS, Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Villaret DB. Malignant tumors of the nasal cavity and paranasal sinuses. *Head Neck.* 2002;24:821-829.
19. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer.* 2001;92:3012-3029.
20. Lavertu P, Roberts JK, Kraus DH, et al. Squamous cell carcinoma of the paranasal sinuses: the Cleveland Clinic experience 1977-1986. *Laryngoscope.* 1989;99:1130-1136.
21. Spiro JD, Soo KC, Spiro RH. Squamous carcinoma of the nasal cavity and paranasal sinuses. *Am J Surg.* 1989;158: 328-332.
22. Paulino AC, Marks JE, Bricker P, Melian E, Reddy SP, Emami B. Results of treatment of patients with maxillary sinus carcinoma. *Cancer.* 1998;83:457-465.
23. Myers LL, Nussenbaum B, Bradford CR, Teknos TN, Esclamado RM, Wolf GT. Paranasal sinus malignancies: an 18-year single institution experience. *Laryngoscope.* 2002; 112:1964-1969.
24. Hoppe BS, Nelson CJ, Gomez DR, et al. Unresectable carcinoma of the paranasal sinuses: outcomes and toxicities. *Int J Radiat Oncol Biol Phys.* 2008;72:763-769.
25. Harrison LB, Raben A, Pfister DG, et al. A prospective phase II trial of concomitant chemotherapy and radiotherapy with delayed accelerated fractionation in unresectable tumors of the head and neck. *Head Neck.* 1998;20:497-503.
26. Rosen A, Vokes EE, Scher N, Haraf D, Weichselbaum RR, Panje WR. Locoregionally advanced paranasal sinus carcinoma. Favorable survival with multimodality therapy. *Arch Otolaryngol Head Neck Surg.* 1993;119:743-746.
27. Wong RJ, Kraus DH. Cancer of the nasal cavity and paranasal sinuses. In: Shah JP, ed. Cancer of the Head and Neck. Hamilton, Ontario: BC Decker, Inc; 2001:204-224.
28. Foote RL, Kasperbauer JL, Okuno SH, et al. A pilot study of high-dose intraarterial cisplatin chemotherapy with concomitant accelerated radiotherapy for patients with previously untreated T4 and selected patients with T3N0-N3M0 squamous cell carcinoma of the upper aerodigestive tract. *Cancer.* 2005;103:559-568.
29. Papadimitrakopoulou VA, Ginsberg LE, Garden AS, et al. Intraarterial cisplatin with intravenous paclitaxel and ifosfamide as an organ-preservation approach in patients with paranasal sinus carcinoma. *Cancer.* 2003;98:2214-2223.

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SBRT of lung cancer

Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy ☆

Gerben R. Borst [a], Masayori Ishikawa [b], Jasper Nijkamp [a], Michael Hauptmann [c], Hiroki Shirato [b], Rikiya Onimaru [b], Michel M. van den Heuvel [d], Jose Belderbos [a], Joos V. Lebesque [a], Jan-Jakob Sonke [a,*]

[a] Department of Radiation Oncology, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[b] Department of Radiation Oncology, Hokkaido University School of Medicine, Sapporo, Japan
[c] Department of Bioinformatics and Statistics, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[d] Department of Thoracic Oncology, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

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ABSTRACT

Purpose: We evaluated the relationship between the mean lung dose (MLD) and the incidence of radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT), and compared this with conventional fractionated radiation therapy (CFRT).
Materials and methods: For both SBRT ($n = 128$) and CFRT ($n = 142$) patients, RP grade $\geqslant 2$ was scored. Toxicity models predicting the probability of RP as a function of the MLD were fitted using maximum log likelihood analysis. The MLD was NTD (Normalized Total Dose) corrected using an α/β ratio of 3 Gy.
Results: SBRT patients were treated with 6–12 Gy per fraction with a median MLD of 6.4 Gy (range: 1.5–26.5 Gy). CFRT patients were treated with 2 Gy or 2.25 Gy per fraction, the median MLD was 13.2 Gy (range: 3.0–23.0 Gy). The crude incidence rates of RP were 10.9% and 17.6% for the SBRT and CFRT patients, respectively. A significant dose–response relationship for RP was found after SBRT, which was not significantly different from the dose–response relationship for CFRT ($p = 0.18$).
Conclusion: We derived a significant dose–response relationship between the risk of RP and the MLD for SBRT from the clinical data. This relation was not significantly different from the dose–response relation for CFRT, although statistical analysis was hampered by the low number of patients in the high dose range.

Stereotactic body radiation therapy (SBRT) for pulmonary lesions is becoming more widely used following the first clinical experiences described by Blomgren et al. in 1995 [1]. Collaboration of Japanese radiation departments resulted in the publication of encouraging outcomes among stage I lung cancer patients after SBRT [2,3]. In addition, SBRT proved to be an effective treatment for metastases in lung and liver with high tumour control rates being achieved [4,5]. With respect to healthy tissue injury, Timmerman et al. [6] observed a significantly higher toxicity for centrally located tumours compared to peripherally located tumours using similar irradiation schedules. In an analysis of Lagerwaard et al. [7], lowering the fraction dose for centrally located tumours resulted in similar toxicity for central and peripheral tumours. A recent review of Brock et al. [8] evaluating SBRT studies showed limited toxicity, whereas a large heterogeneity of treatment techniques, dose parameters and clinical endpoints is observed between these studies. To extend the applicability of SBRT, knowledge of the dose–toxicity relationship is necessary. However, dose–response evaluations are hampered by the restricted dose range and (consequently) the low number of toxicity events following SBRT. Moreover, the influence of larger fraction dose, shorter overall treatment time and differences in dose distribution on the existing radiobiological models is rather unknown. In addition, patients receiving pulmonary SBRT are a select group of patients with a high comorbidity.

Radiation pneumonitis (RP) is a serious complication which was fatal after SBRT in three of the 25 patients in a recent study of Yamashita et al. [9] after 48 Gy in four fractions. The incidence of RP requiring clinical intervention ranges from 0% to 29% after SBRT [9–14]. Unfortunately, no predictive model to assess the probability of RP is available for SBRT.

The goal of our study was to evaluate the relation between the radiation dose and the occurrence of RP after SBRT. In addition,

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* Corresponding author. Address: Department of Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands.
E-mail address: j.sonke@nki.nl (J.-J. Sonke).

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since the relation between lung dose and radiation pneumonitis (RP) is extensively evaluated for CFRT (e.g. [15]), we compared the dose relationship of SBRT and CFRT patients.

Materials & methods

Patients

SBRT patients were irradiated with hypofractionated schedules at the Department of Radiation Medicine of the Hokkaido University School of Medicine, Sapporo, Japan. Clinical data and treatment plans were retrievable for 128 patients treated between April 1998 and December 2005. Follow-up was performed at the outpatient clinic of the Department of Radiation Medicine. Irradiation regimens were 35 Gy in four fractions, 40 Gy in four fractions, 48 Gy in eight fractions, 60 Gy in eight fractions and 48 Gy in four fractions. A subgroup of these patients with a schedule of 40 and 48 Gy in four fractions (n =41) was previously described in a tumour dose–response study [16]. The approach to define appropriate doses and margins for the SBRT patients can be described as a continuous reassessment approach which was dependent on tumour control and toxicity. This has been accurately described previously [16]. Patients with a schedule of 35 Gy in four fractions, 48 and 60 Gy in eight fractions (irradiated before 2000) and patients treated for multiple targets were treated in a similar manner.

Ninety-five SBRT patients were irradiated on one single target. The treatment schedule, diagnosis of RP and the MLD of these patients are listed out in Table 1. Thirty-three patients received irradiations on multiple targets. For 20 patients, the initial radiation treatment consisted of multiple targets that were successively treated (Table 2). For 13 patients, a new treatment plan was made sometime after the initial treatment because of additional pulmonary lesions (Table 3). No time-related recovery of lung tissue was taken into account for these 13 patients. These 33 patients received an individually adapted (i.e. restricted) dose schedule. For all plans (and summed plans in case of re-irradiations), a maximum dose of 46 and 60 Gy (recalculated into 2 Gy per fraction with an α/β ratio of 2 Gy) for the spinal cord and oesophagus, respectively, was allowed. A total dose of 60 Gy/8fr or equivalent dose calculated using LQ model with an α/β ratio = 2 Gy was allowed as maximum dose in the lung.

Patients with a conventional dose per fraction (CFRT) schedule were treated at the Department of Radiation Oncology of the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, The Netherlands. We updated our previous analysis (with 106 patients) by Seppenwoolde [17] to a total of 142 patients. Our update included 86 patients of the dose escalation (DE) study of Belderbos et al. [17]) (with 88 patients). For two patients included in this study, dose data were lost. Of the 58 non-DE patients included in the Seppenwoolde study, we excluded two patients, whose treatment was interrupted and not finished. Therefore, we were able to include 86 patients of the DE study (who were irradiated to a dose of 60.8 and 94.5 Gy with 2.25 Gy per fraction), and 56 patients who were irradiated with a dose of 70 Gy in 2 Gy per fraction.

For both SBRT and CFRT patients, three dimensional (3-D) treatment plans were made. To correct for the effect of dose per fraction, the local dose was converted to the 2 Gy equivalent Normalized Total Dose (NTD) [18] using the linear quadratic (LQ) model [19] with an α/β ratio of 3 Gy. The α/β ratio of 3 Gy was used because in coventional schemes this commonly used [20] and detailed analysis revealed that for SBRT this was the best value to correct for the dose per fraction evaluating RP (data not shown). For the 33 SBRT patients irradiated on multiple lesions, individual plans were summed after NTD corrections and image registration had been performed. From the 3-D dose data, the MLD was calculated as the average corrected dose over the total lung volume (based on CT) excluding the gross tumour volume.

For the SBRT plans, a convolution superposition algorithm for tissue density heterogeneity was used. For the CFRT patients, the inhomogeneity correction was performed using the equivalent-path length (EPL) inhomogeneity correction. The MLD_{EPL} was converted to the MLD according to convolution superposition algorithm using the conversion factor determined by De Jaeger et al. ($MLD = 0.64(MLD_{EPL})^{1.10}$) [21].

The dose–response relationship in the lungs between RP and MLD was modelled by a sigmoid-shaped relation according to Lyman [22] using the TD_{50} representing the dose for a 50% complication probability. The slope of the dose–response relationship is proportional to the reciprocal value of $m{\cdot}TD_{50}$. Using this model and parameter values, the normal tissue complication probability (NTCP) (i.e. RP) can be calculated from the MLD [23].

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \text{ with } t = \frac{MLD - TD_{50}}{m \cdot TD_{50}}$$

Radiation pneumonitis (RP) was prospectively scored for both SBRT and CFRT patients and was classified according to the NCI-CTC (CTC 2.0) or SWOG criteria. Grade 2 RP was scored for both SBRT and CFRT after steroids had been prescribed for RP symptoms. Grade 3 RP was scored after oxygen was required, and grade 4 was scored for assisted ventilation. Grade 5 was scored after death due to RP.

None of the included SBRT patients who were scored with RP grade 2 used steroids for other pulmonary morbidities than for RP before or after the irradiation. For the CFRT patients, information on pre-treatment use of steroids was not available. For all patients, the diagnosis and grade of RP were determined by the radiation oncologist and by a pulmonologist experienced in the diagnosis of RP.

Statistics

By maximizing the logarithm of the likelihood function of a dataset containing N patients

$$\ln(L) = \ln\left(\prod_{i=1}^{N} L_i\right) = \sum_{i=1}^{N} \ln(L_i)$$
$$= \sum_{i=1}^{N} [ep_i \ln(P_i) + (1 - ep_i) \ln(1 - P_i)],$$

Table 1
The total dose, fraction dose, median tumour volume, median MLD, and the incidence of RP for each treatment schedule of the SBRT patients.

Number of patients	Total dose (Gy)	Fraction dose (Gy)	Median tumour volume (cm^3)	Median MLD (Gy)	Number of RP
3	35	8.75	32.8	5.1	1
29	40	10	15.9	5.4	2
15	48	6	12.0	5.5	0
39	48	12	7.7	7.0	4
9	60	7.5	2.6	3.5	0
20	>2 successively treated lesions		19.5	10.1	5
13	>2 treated lesions (minimum time interval of 2.8 months)		30.6	7.5	2

Table 2
Treatment schedule, number of irradiated targets, diagnosis of RP, and the MLD of SBRT patients with multiple targets incorporated in one single treatment plan.

Pt	Number of targets	D 1 (Gy)	fr 1	D 2 (Gy)	fr 2	D 3 (Gy)	fr 3	RP	MLD (Gy)
1	2	48	8	48	12				5.5
2	2	40	4	35	4			+	8.0
3	2	48	8	48	8				16.1
4	2	48	4	48	4			+	15.8
5	2	48	4	48	8			+	19.2
6	2	40	4	40	4				17.0
7	2	48	4	48	4				11.0
8	2	40	4	40	4				11.0
9	2	40	4	40	4				8.9
10	2	35	4	35	4				3.7
11	2	35	4	45	15				6.4
12	2	60	8	60	8				4.5
13	2	40	4	50	16				6.9
14	2	48	4	40	8				11.1
15	2	48	8	48	8				10.7
16	2	48	4	60	8			+	10.3
17	2	48	4	48	4				6.9
18	2	48	8	48	8			+	16.2
19	3	40	4	40	4	48	8		5.3
20	3	40	8	35	4	35	4		7.1

Table 3
Treatment schedule, time between subsequent treatments, diagnosis of RP and the MLD of SBRT patients with multiple targets incorporated in different treatment plans.

Pt	Number of treatments	D 1 (Gy)	fr 1	D 2 (Gy)	fr 2	Time 2 (mths)	D 3 (Gy)	fr 3	Time 3 (mths)	D 4 (Gy)	fr 4	Time 4 (mths)	RP	MLD (Gy)
1	2	48	8	30	8	13.3								7.6
2	2	35	4	40	4	9.8								8.9
3	2	40	4	30	8	8.3							+	7.5
4	2	40	4	35	4	4.4								9.2
5	2	60	8	40	4	2.8								8.6
6	3	48	8	35	8	6.3	48	8	6.7				+	18.1
7	3	48	4	30	10	1.4	48	8	13.2					20.6
8	3	60	8	60	8	0.6	60	8	9.1					9.7
9	3	48	8	25	5	0.1	25	5	16.9					8.4
10	4	60	8	40	4	0.7	48	8	10.8	25	5	15.7		13.3
11	4	60	8	35	4	9.7	35	4	9.7	35	4	9.7		10.6
12	4	40	4	40	4	0.1	40	4	0.6	40	4	3.3		26.5
13	4	60	8	48	8	0.0	48	8	21.5	35	4	28.8		13.5

where P_i ($i = 1, \ldots, N$) represents the NTCP of a patient i, and ep_i is the binary outcome (0 = no RP, 1 = RP), the parameters TD_{50} and m of the NTCP model were estimated. Ninety-five percent confidence intervals around m and TD_{50} were calculated using a profile likelihood approach [22]. For each parameter, the confidence interval includes a certain value if twice the difference of the log likelihood evaluated at the maximum likelihood estimate and at the value of interest does not exceed the quantile of a chi-square (χ^2) distribution with one degree of freedom [24]. To determine the confidence interval of the NTCP curve, a similar approach was performed, however, this test was performed with two degrees of freedom.

To test the difference between the fitted NTCP model of SBRT and CFRT, the data of both models were pooled. The NTCP model based on the pooled data (i.e. one TD_{50} and one m) was compared to the NTCP model, whereby the dataset-specific optimized parameters of SBRT and CFRT were included in a two degree of freedom likelihood ratio test [22].

We also compared the empirical incidence of RP across datasets for several non-overlapping dose intervals using Fisher's exact test.

The Hosmer–Lemeshow goodness-of-fit test [25] was used to estimate the goodness of the fit of the fitted NTCP model. Patients were divided into 10 equal bins in increasing order of the estimated NTCP. The χ^2 test statistic was calculated by

$$\chi^2_{HL} = \sum_{i=1}^{10} \frac{(O_i - N_i \cdot \overline{NTCP_i})^2}{N_i \cdot \overline{NTCP_i} \cdot (1 - \overline{NTCP_i})}$$

where N_i is the total number of patients in the ith group, O_i is the total number of events in the ith group, and $\overline{NTCP_i}$ is the mean calculated NTCP in the ith group. The test statistic is compared to a χ^2 distribution with eight degrees of freedom (by definition of the Hosmer–Lemeshow goodness-of-fit test). The null hypothesis is that there is no difference between the observed and expected values of RP. (i.e. large values of χ^2 (and small p values) indicate a lack of fit by the model).

A two-tailed $p < 0.05$ was considered to be statistically significant.

Results

Radiation pneumonitis

Median follow-up was 16.1 months for the SBRT patients and was 13.0 months for the CFRT patients. All 39 events occurred within 6.2 months following treatment for both SBRT and CFRT within a similar time frame. Within this period, four SBRT patients and 18 CFRT patients were censored (Fig. 1).

For SBRT, the crude incidence of RP grade 2 or higher was 10.9% (14 events in the group of 128 patients). Only one SBRT patient was diagnosed with grade 3 RP. Three SBRT patients included in the analysis, received oxygen within the first year after irradiation, and were not scored as having RP because of the uncertainty of diagnosis (one patient had cardiac problems, one patient had a

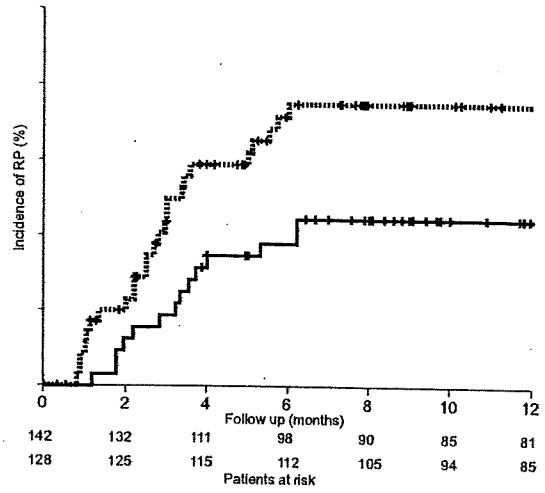

Fig. 1. The incidence of RP as a function of the follow-up (months). Vertical axis: one minus the cumulative RP-free survival. Censored patients are indicated by crosses. The follow-up is given in months on the horizontal axis.

medical history of receiving oxygen before treatment and one patient had fibrosis and tumour progression).

For CFRT, the crude incidence of RP was 17.6% (25 events in the group of 142 patients). Four CFRT patients experienced a grade 3 RP, and one patient died due to pulmonary toxicity (grade 5 RP).

Tumour volume and mean lung dose

The median MLD for SBRT was 6.4 Gy (range: 1.5–26.5 Gy). The median tumour volume of the SBRT patients was 9.6 cm^3 (range: 0.2–106.9 cm^3). For CFRT patients, the median MLD was 13.2 Gy (range: 3.0–23.0 Gy) and the median tumour volume was 61.2 cm^3 (range: 3.8–789.9 cm^3).

Normal tissue complication probability

SBRT

For SBRT, the observed incidence of RP as a function of the MLD is plotted in Fig. 2a. The error bars represent the 68% confidence interval (CI) of the observed incidence in 4 Gy dose bins. The observed number of RP and the total number of patients within each dose bin are indicated. The solid line represents the best fit of the NTCP model based on the MLD. The best parameter values of the NTCP model were $TD_{50} = 19.6$ Gy (95% CI: 16.0–30.0 Gy) and $m = 0.43$ (95% CI: 0.33–0.59). The dashed lines represent the 68% CI of the fitted curve.

CFRT

For CFRT, the observed incidence of RP as a function of the MLD is plotted in Fig. 2b. The optimal fit of the NTCP model using MLD resulted in a TD_{50} of 28.6 Gy (95% CI: 21.5–125.0 Gy) and in an m value of 0.56 (95% CI: 0.39–0.99).

SBRT versus CFRT

Both the SBRT model and the CFRT model fitted the clinical data well ($\chi^2_{HL} = 8.27$, $p = 0.41$ and $\chi^2_{HL} = 4.36$, $p = 0.82$, respectively).

A comparison of the dose-specific observed RP incidence between SBRT and CFRT revealed that there was no significant difference for any of the six dose ranges covering 4 Gy each. However, RP occurred more frequently in the two highest dose ranges for SBRT compared to CFRT, but this difference was not significant (Table 4). Importantly, lower numbers of patients were included in the higher dose ranges for both SBRT and CFRT, limiting the power of statistical comparison of these particular high dose groups.

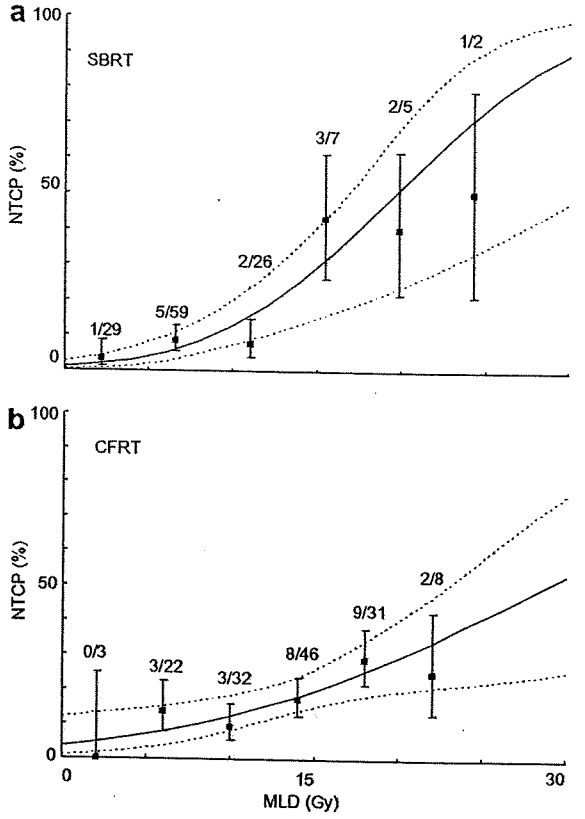

Fig. 2. (a and b) The incidence of grade ⩾2 RP of SBRT (2a)- and CFRT (2b)-irradiated patients as a function of the MLD. The error bars represent the 68% confidence intervals (CIs) of the observed incidence. The solid lines represent the probability of RP according to the NTCP model with the optimized parameters m and TD_{50}. The dotted lines represent the 68% CI of the fitted NTCP curve.

Table 4
Incidence of RP by MLD range and treatment type (SBRT and CFRT).

Dose bin (Gy)	SBRT Number of RP events/total number of patients	CFRT Number of RP events/total number of patients	*p*-value Fisher's exact test
0–4	0/23 (0%)	0/3 (0%)	0.99
4–8	4/60 (7%)	3/22 (14%)	0.38
8–12	4/28 (14%)	3/32 (9%)	0.70
12–16	1/8 (13%)	4/46 (9%)	0.99
16–20	4/7 (57%)	9/31 (29%)	0.20
20–28	1/2 (50%)	2/8 (25%)	0.46

On evaluating the whole dose range, the NTCP curve of SBRT is steeper for the high dose range suggesting an increased risk for RP after SBRT compared to CFRT for patients with a higher MLD. However, there was no statistical evidence that the fitted NTCP model (with the parameters m and TD_{50}) differed between SBRT and CFRT ($p = 0.37$, likelihood ratio test). Again, we would like to stress that the statistical power was limited due to lower number of patients in the high dose range.

The optimal fit of the SBRT and CFRT together resulted in a TD_{50} of 24.4 Gy (95% CI: 21.0–32.0 Gy) and in m of 0.49 (95% CI: 0.42–0.61) (Fig. 3).

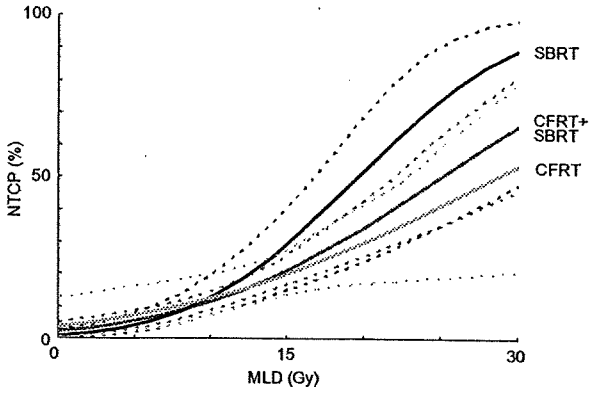

Fig. 3. Fitted NTCP curves (solid lines) and their 68 % confidence intervals (CI) intervals (dashed lines) as a function of the MLD for SBRT (dark grey), CFRT (black) and combined data (light grey) (coloured version available online).

Discussion

A significant relationship between the MLD and the incidence of RP following SBRT was observed. Moreover, the NTCP model fitted the SBRT data well. We observed no significant difference between the NTCP models predicting RP in SBRT and CFRT patients. Furthermore, no significant difference between SBRT and CFRT was observed in the incidence of RP in any dose range. Nevertheless, an increased risk for SBRT in higher dose ranges was suggested by both the NTCP model fit and the observed RP incidences. However, because fewer patients were available in the high dose range no firm conclusions can be made concerning these differences.

At the Department of Radiation Medicine of the Hokkaido University School of Medicine, different SBRT dose schedules have been used since 1998. The first applied schedule was 35 Gy in four fractions which was escalated to 48 Gy in four fractions. Between these schedules, interim doses of 40 Gy in four fractions and 48 and 60 Gy in eight fractions were given. In addition, tumours located near to critical structures were more fractionated than peripheral tumours. The absence of severe toxicity strengthened the approach of re-treating patients with tumour recurrence or irradiating multiple lesions sequentially. Consequently, a dose–response analysis could be performed with a dose range similar to the dose range of the CFRT. The comparison of SBRT with CFRT was performed with an update of previously evaluated NKI-AVL CFRT patients. As expected, the m and TD_{50} for these CFRT patients were similar to a previous publication [18] and the meta-analysis of Semenenko and Li [15].

Previous SBRT studies reported a 0% to 29% incidence of RP grade 2 or higher [3,9–14,26]. Unfortunately, only a limited number of studies reported dose parameters to describe the lung dose. Yamashita et al. [9] reported a high incidence of RP grade 2 or higher in seven of the 25 patients treated with 48 Gy in four fractions. The mean MLD was only 4.3 Gy (ranging from 1.72 Gy to 5.85 Gy). However, for the calculation of the lung dose, which was not NTD corrected, not only the tumour volume was subtracted from the total lung volume, but also an extra margin surrounding the tumour was subtracted, resulting in an underestimation of the lung dose. Nagata et al. [13] reported a 4% incidence of RP grade 2 in patients treated with 48 Gy in four fractions with a mean V20 (percentage volume of the whole lung receiving more than 20 Gy) in this patient group of only 4.5%. In the study by Ng et al. [26], no RP grade 2 or higher was observed. However, this study included only 20 patients with 80% of the patients having a V20 < 20% (GTV ranged from 4.27 to 74 cm^3).

The clinical applicability of our results in relation to other SBRT schedules may be questionable as many institutions in Europe and the USA use fraction doses of 18 Gy or 20 Gy. In our study, 48 Gy in four fractions was the most commonly used fractionation schedule having eight different beam angles (i.e. 1.5 Gy per beam). For fraction doses of 18 Gy, at least 12 different beam angles are used [6], which also results in 1.5 Gy per beam. Therefore, the major part of the lung tissue will receive equivalent doses per fraction. Moreover, in the 18 Gy or 20 Gy per fraction schedule, the percentage of lung tissue receiving the highest proportion of the dose is small because smaller dose planning margins of 5 to 10 mm around the tumour are used [6] (most of our patients had 11 to 13 mm margins [16]). Therefore, large deviations in the lung tissue response of these hypofractionated schedules are not expected.

Because the collaboration encompassed two different radiotherapy departments, a lot of effort was invested in standardizing methods for dose planning and dose calculation between the patient groups. A recent study by Gershkevish [27] showed that deviations between different treatment planning systems decrease with the use of more advanced calculation algorithms. For all patients included in this analysis, the superposition or collapsed cone algorithm was used for treatment planning. The clinical variability in the prescribing of steroids between the two institutes was limited as only patients who were diagnosed by both radiotherapists and pulmonologists experienced with the diagnosis of radiation pneumonitis were included. Patients were excluded if the diagnosis of RP was hampered or was accompanied by pulmonary comorbidity (e.g. infection, tumour progression, and previous use of oxygen). Nevertheless, the uncertainties of including patients from two different institutes should be taken into account, and a similar one single-institute validation would be of interest.

We observed a similar time frame for RP occurrences in both SBRT and CFRT; RP occurred several weeks to 6 months after irradiation as both Guckenberger et al. [10] and Yamshita et al. [9] reported for SBRT, and as Graham et al. [28] reported for CFRT. Further toxicity may be observed with a longer follow-up. In the study by Timmerman et al. [6], four of the six treatment-related deaths occurred after 12 months. Four of the patients suffered from a bacterial pneumonia, and one patient experienced tumour recurrence adjacent to the carina. Evidently, both short- and long-term toxicity may conceivably be obscured by pulmonary comorbidity or tumour progression. Therefore, these patients, who are often suffering from pulmonary comorbidities, should be intensively followed up by both radiation oncologists and pulmonologists.

For lung cancer patients or patients with pulmonary metastases, the critical prognostic importance of controlling RP risks must be balanced not only against the patient's physical condition, but also against tumour control. A strong consequential component between acute and long-term pulmonary toxicity after lung irradiation is observed in animal studies [29,30]. Consequently, even though grade 2 RP might not be life threatening, it may substantially contribute to a cascade of pulmonary deterioration in patients with pulmonary comorbidity. Moreover, a long-term dose-dependent progressive decline of pulmonary function is observed in patients treated with CFRT [31] with MLD up to 21.9 Gy (mean MLD 13.9 Gy). In a recently published SBRT phase II study [32], no relationship was observed between toxicity and lung dose. In this study, a mean MLD of 7 Gy for 60 patients was found. Our retrospective study encompassed a larger dose range for a larger number of patients, but no pulmonary function data or follow-up CTs were evaluated. A prospective study with a large dose range with long-term follow-up should reveal the predictability of any radiation-induced toxicity after hypofractionated schedules.

To date, there are no clinical data available which compare the prognosis (survival) of lung cancer patients experiencing clinically

relevant radiation-induced toxicity versus non-symptomatic patients. With regard to the optimal treatment, the clinical evaluation of the risk of tumour recurrence and of the probability of toxicity is a matter of concern in a patient group with a poor tumour-related prognosis and a high incidence of comorbidity. Our retrospective evaluation can serve as a guideline estimating the probability of RP for the clinical decision making (i.e. staying on the safe side for pulmonary compromised or palliative patients and accepting a higher risk of toxicity for curable patients without pulmonary comorbidities). Nevertheless, prospective studies are needed to reveal the relation of short- and long-term toxicity and tumour control.

Time-related recovery of lung tissue was not taken into account in our patients who had received multiple treatment schemes. A mouse study by Terry et al. [33] showed that irradiation-induced lung injury tissue could (partly) recover, suggesting an early target cell depletion and regeneration which was dependent on the size of the initial injury (i.e. dose). For a single dose of 10 Gy, less recovery was observed than for 6 Gy. Clinical studies evaluating toxicity after re-irradiations for lung cancer patients are limited due to poor prognosis. Okamoto et al. [34] studied 34 lung cancer patients re-irradiated because of a local recurrence. The large number of patients (19 patients, i.e. 56%) experiencing grade 2 or higher RP suggest limited (or no) time-related recovery. Moreover, from the long-term survivors (20–58 months after re-irradiation) 71% of the patients experienced a grade 2 RP. However, no lung dose characteristics were reported, and RP risk estimating could therefore not be performed.

To predict normal tissue complication probabilities (NTCPs) after radiotherapy treatment, the delivered dose has to be recalculated into a biological-effective dose using a mathematical model (linear quadratic model) [35,36] derived from in vitro and animal studies [37]. The clinical applicability of this model is a historical cornerstone in assessing tumour doses and dose tolerance of normal tissues in conventional fractionation schemes. In contrast, no study validated the clinical applicability of the LQ model for hypofractionation. For NSCLC cell lines and animal iso-effect data modifications of the LQ model were proposed showing an improved description of the dose response relation using these models [38,39]. Further evaluation concerning the LQ model and potential modifications of the LQ model to calculate the biological-effective dose in clinical setting for hypofractionated schedules is therefore warranted.

Although there were numerous limitations in our study, we were able to show a relationship between the lung dose and the incidence of RP for SBRT that was not significantly different from CFRT.

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References

[1] Blomgren H, Lax I, Naslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861–70.
[2] Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623–31.
[3] Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94–S100.
[4] Wulf J, Haedinger U, Oppitz U, et al. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys 2004;60:186–96.
[5] Timmerman RD, Kavanagh BD, Cho LC, et al. Stereotactic body radiation therapy in multiple organ sites. J Clin Oncol 2007;25:947–52.
[6] Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833–9.
[7] Lagerwaard FJ, Haasbeek CJ, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;70:685–92.
[8] Brock J, Ashley S, Bedford J, et al. Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer 1. Clin Oncol (R Coll Radiol) 2008;20:666–76.
[9] Yamashita H, Nakagawa K, Nakamura N, et al. Exceptionally high incidence of symptomatic grade 2–5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. Radiat Oncol 2007;2:21.
[10] Guckenberger M, Heilman K, Wulf J, et al. Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol 2007;85:435–42.
[11] Zimmermann FB, Geinitz H, Schill S, et al. Stereotactic hypofractionated radiotherapy in stage I (T1–2 N0 M0) non-small-cell lung cancer (NSCLC). Acta Oncol 2006;45:796–801.
[12] Aoki T, Nagata Y, Negoro Y, et al. Evaluation of lung injury after three-dimensional conformal stereotactic radiation therapy for solitary lung tumors: CT appearance 106. Radiology 2003.
[13] Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys 2005;63:1427–31.
[14] McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010–5.
[15] Semenenko VA, Li XA. Lyman–Kutcher–Burman NTCP model parameters for radiation pneumonitis and xerostomia based on combined analysis of published clinical data. Phys Med Biol 2008;53:737–55.
[16] Onimaru R, Fujino M, Yamazaki K, et al. Steep dose–response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy. Int J Radiat Oncol Biol Phys 2008;70:374–81.
[17] Belderbos JS, Heemsbergen WD, De Jaeger K, et al. Final results of a phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2006;66:126–34.
[18] Lebesque JV, Keus RB. The simultaneous boost technique: the concept of relative normalized total dose. Radiother Oncol 1991;22:45–55.
[19] Douglas BG, Fowler JF. The effect of multiple small doses of X-rays on skin reactions in the mouse and a basic interpretation. Radiat Res 1976;66:401–26.
[20] Kwa SL, Lebesque JV, Theuws JC, et al. Radiation pneumonitis as a function of mean lung dose: an analysis of pooled data of 540 patients. Int J Radiat Oncol Biol Phys 1998;42:1–9.
[21] De Jaeger K, Hoogeman MS, Engelsman M, et al. Incorporating an improved dose-calculation algorithm in conformal radiotherapy of lung cancer: re-evaluation of dose in normal lung tissue. Radiother Oncol 2003;69:1–10.
[22] Clayton D, Hills M. Statistical models in epidemiology. New York: Oxford University Press; 1993.
[23] Seppenwoolde Y, Lebesque JV, De Jaeger K, et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys 2003;55:724–35.
[24] Venzon DJ, Moolgavkar SH. A method for computing profile-likelihood-based confidence intervals. Appl Stat 1988;37:87–94.
[25] Hosmer D, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat - Theory Models 1980;A9:1043–69.
[26] Ng AW, Tung SY, Wong VY. Hypofractionated stereotactic radiotherapy for medically inoperable stage I non-small cell lung cancer–report on clinical outcome and dose to critical organs. Radiother Oncol 2008;87:24–8.
[27] Gershkevitsh E, Schmidt R, Velez G, et al. Dosimetric verification of radiotherapy treatment planning systems: results of IAEA pilot study. Radiother Oncol 2008.
[28] Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323–9.
[29] Franko AJ, Sharplin J. Development of fibrosis after lung irradiation in relation to inflammation and lung function in a mouse strain prone to fibrosis. Radiat Res 1994;140:347–55.
[30] Trott KR, Herrmann T, Kasper M. Target cells in radiation pneumopathy. Int J Radiat Oncol Biol Phys 2004;58:463–9.
[31] Borst GR, De Jaeger K, Belderbos JS, et al. Pulmonary function changes after radiotherapy in non-small-cell lung cancer patients with long-term disease-free survival. Int J Radiat Oncol Biol Phys 2005;62:639–44.
[32] Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol 2008;88:359–67.