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Multi-institutional retrospective study for the evaluation of ocular function–preservation rates in maxillary sinus squamous cell carcinomas with orbital invasion

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ABSTRACT: *Background.* The purpose of this retrospective analysis was to evaluate ocular function and survival rates among treatment modalities in patients with maxillary sinus cancer with orbital invasion.

Methods. Eighty-seven patients were classified according to the main treatment modality. Ocular function preservation rates and survival rates were evaluated for each therapeutic modality.

Results. The 5-year overall survival rate for the en bloc resection, conservative surgery, superselective intra-arterial chemotherapy, and radiotherapy (RADPLAT), intravenous chemoradiotherapy (IV-CRT) was 70%, 35%, 49%, and 31%, respectively. The ocular function preservation rate for each group was 15%, 27%, 30%, and 17%, respectively. In the en bloc resection group, there was no significant difference in the 5-year overall survival rate between patients with orbital exenteration and those without orbital exenteration (72% vs 71%; $p = .9321$).

Conclusion. The en bloc resection group showed a favorable survival rate but a low preservation rate. Preservation of orbital contents did not reduce the survival rate. © 2014 Wiley Periodicals, Inc. *Head Neck* **00**: 000–000, 2014

KEY WORDS: maxillary sinus cancer, orbital invasion, ocular function, squamous cell carcinoma, chemoradiotherapy

INTRODUCTION

The majority of patients with maxillary sinus cancer are diagnosed in the locally advanced stage. Orbital invasion occurs in 60% to 80% of maxillary sinus malignancies.[1] In such cases, it is still controversial whether the orbital contents should be preserved or not when en bloc surgical resection is indicated. The 2 main points of contention are the oncologic safety of orbital preservation and the functional outcome in the preserved eyes. The indications and need for orbital exenteration have recently evolved with improvements in diagnostic imaging modalities. It was reported that orbital preservation was oncologically safe in selected cases and did not reduce the rate of cure or local control.[1,2]

In addition, Nishino et al[3,4] reported the results of conservative surgery combined with radiotherapy and chemotherapy, in which 2-stage surgical treatments, including antrostomy and minimally invasive segmental maxillary resection, were performed for the purpose of preserving maxilla and ocular function. This conservative multidisciplinary therapy was reported to be feasible for the treatment of advanced maxillary sinus cancer and enable preservation of orbital contents by use of a surgical microscope.

Further, superselective intra-arterial chemotherapy and concomitant radiotherapy (RADPLAT) has been attempted for preserving the orbital contents and ocular function in patients with advanced maxillary sinus cancer. This nonsurgical treatment was reported to be both safe and highly effective.[5,6]

There have been no reports on survival rates and ocular function among the various treatment modalities because of the low incidence of maxillary sinus cancer. Recently, a multi-institutional joint research program for maxillary

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TABLE 1. Patient demographics.

Characteristic	No. of patients (%)
Total	87
Sex	
Male	63 (72)
Female	24 (28)
Age, y	
Median	65
Range	30–84 (Avg. 63.6)
Follow-up period, mo	
Median	52.0
Range	6.0–71.8 (Avg. 46.3)
T classification	
T4a	49 (56)
T4b	38 (44)
N classification	
N0	73 (84)
N1	5 (6)
N2a–c	9 (10)
N3	0 (0)

sinus cancer was undertaken in Japan. Twenty-eight institutions participated in this research and the data for 128 patients were obtained. The purpose of this analysis was to evaluate ocular function–preservation rates and survival rates among treatment modalities in patients with maxillary sinus cancer with orbital invasion.

MATERIALS AND METHODS

The data for 128 patients with previously untreated maxillary sinus squamous cell carcinomas between January 2006 and December 2007 were obtained from 28 institutions belonging to the Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG). The therapeutic strategy varied widely among the institutions. The maxillary sinus cancer involved the orbital contents in 94 patients. Of these 94 patients, 5 patients underwent palliative therapy because of distant metastasis or their general condition. In addition, 2 patients were treated at other institutions for their wishes. These 7 patients were excluded from the analysis. The remaining 87 patients were eligible for this study. Table 1 shows patient demographics.

This was a retrospective analysis. Therefore, the selection criteria for therapeutic modality were decided according to the policy of each institution or individual patient preference. This multi-institutional joint research has been representatively approved by the appropriate ethical committees in the National Hospital Organization Tokyo Medical Center, Tokyo, Japan.

Eighty-seven patients were classified according to the main treatment modality under 5 categories, such as the en bloc resection group, the conservative surgery group, the RADPLAT group, the intra-venous chemoradiotherapy (IV-CRT) group, and the radiation alone group. The en bloc resection group consisted of patients undergoing total maxillectomy with or without orbital exenteration. The conservative surgery consisted of 2-stage conservative surgery, combining antrostomy and minimally invasive segmental maxillary resection with radiotherapy and chemotherapy.[3,4]

After a previously published report,[2] ocular function was assessed using basic clinical parameters: day-to-day use of the eye, subjective change in visual acuity, diplopia, gross visual fields, exposure keratitis, blepharitis or conjunctivitis, lacrimal system dysfunction, and so on. Ocular function was graded as functional vision without impairment (no persistent ophthalmologic sequelae), functional vision with impairment (1 or more significant chronic ophthalmologic sequelae), nonfunctional (blindness, light-perception only, nonserviceable visual acuity, or intractable diplopia), or totally removed on the basis of the medical records at the end of observation (median, 52 months posttreatment).

The Kaplan–Meier method was applied for the analysis of survival and local control rates, and the survival and local control rates were compared using the log-rank test. The time of interest for survival and local control rates was the period from the start of treatment to death or failure. The time of interest for preservation of ocular function was the period from the start of treatment to death, removal of orbital contents, or loss of ocular function. A p value of $< .05$ was considered statistically significant. JMP Pro 10.0.0 statistical software (SAS Institute, Cary, NC) was used for the statistical analysis.

RESULTS

A total of 33 of 87 patients (38%) were categorized into en bloc resection group. En bloc resection without orbital exenteration was performed for 7 patients. En bloc resection with orbital exenteration was performed for 16 patients. En bloc resection with anterior craniotomy and orbital exenteration was performed for 9 patients. In 1 patient, en bloc resection was planned after preoperative chemotherapy and radiotherapy. However, this patient refused en bloc resection before surgery and he was irradiated with a total of 70 Gray (Gy). This case was categorized into the en bloc resection group for intention-to-treat analysis.

A further 15 patients (17%) underwent conservative surgery, 21 patients (24%) underwent RADPLAT, 14 patients (16%) underwent IV-CRT, and 4 patients (5%) underwent radiation alone. Of the 33 patients in the en bloc resection group, 26 patients (79%) were classified as T4a. In addition, 11 patients (73%) undergoing conservative surgery, 5 patients (24%) undergoing RADPLAT, and 5 patients (36%) undergoing IV-CRT were classified as T4a. Adjunctive radiotherapy and adjunctive chemotherapy was performed in 91% (30 of 33) and 73% (24 of 33) of patients undergoing en bloc resection, respectively. All patients in the conservative surgery group underwent adjunctive radiotherapy, and adjunctive chemotherapy was performed in 87% of patients in this group (Table 2). Details of the tumor-involved orbital sites are shown in Table 3. The orbital apex was involved in 57% of the RADPLAT group.

Table 4 shows the evaluation of ocular function. In 25 of 33 patients in the en bloc resection group, orbital exenteration was performed. One patient undergoing RADPLAT needed total maxillectomy and orbital exenteration 4 months after the completion of RADPLAT

TABLE 2. TN classification and adjunctive treatment.

	No. of patients	T classification		N classification		Adjunctive treatment	
		T4a	T4b	N0	N > 1	Radiotherapy	Chemotherapy
En bloc resection	33	26 (79%)	7 (21%)	30 (91%)	3 (9%)	30 (91%)	24 (73%)
Conservative surgery	15	11 (73%)	4 (27%)	12 (80%)	3 (20%)	15 (100%)	13 (87%)
RADPLAT	21	5 (24%)	16 (76%)	17 (81%)	4 (19%)	–	5 (24%)
IV-CRT	14	5 (36%)	9 (64%)	12 (86%)	2 (14%)	–	2 (14%)
Radiation alone	4	2 (50%)	2 (50%)	2 (50%)	2 (50%)	–	1 (25%)

Abbreviations: RADPLAT, intra-arterial chemotherapy, and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

TABLE 3. Details of tumor-involved orbital sites.

	No. of patients	Tumor-involved orbital sites			
		Anterior orbit	External eye muscle	Fat tissue	Orbital apex
En bloc resection group	33	27 (82%)	16 (48%)	28 (85%)	4 (12%)
Without orbital exenteration	7	7 (100%)	1 (14%)	5 (71%)	0 (0%)
With orbital exenteration	16	14 (88%)	9 (56%)	14 (88%)	1 (6%)
With craniotomy and orbital exenteration	9	5 (56%)	6 (67%)	8 (89%)	3 (33%)
Not performed	1	1 (100%)	0 (0%)	1 (100%)	0 (0%)
Conservative surgery group	15	11 (73%)	5 (33%)	10 (67%)	4 (27%)
RADPLAT group	21	19 (90%)	8 (38%)	15 (71%)	12 (57%)
IV-CRT group	14	10 (71%)	9 (64%)	10 (71%)	6 (43%)
Radiation alone group	4	2 (50%)	2 (50%)	4 (100%)	1 (25%)

Abbreviations: RADPLAT, intra-arterial chemotherapy, and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

because of primary tumor recurrence. One patient in the IV-CRT group had an ocular problem before the onset of maxillary cancer, and ocular function was not recorded in another patient in this group. These 2 patients were excluded from the evaluation of ocular function.

Figure 1 indicates the overall survival rate curves for treatment modalities. The 5-year overall survival rates of all 87 patients, the en bloc resection group, the conservative surgery group, the RADPLAT group, and the IV-CRT group were 47%, 70%, 35%, 49%, and 31%, respectively. All 4 patients undergoing radiation alone died within 2 years of the start of treatment.

Figure 2 indicates the local control rate curves for treatment modalities. The 5-year local control rates of all 87 patients, the en bloc resection group, the conservative surgery group, the RADPLAT group, and the IV-CRT group were 45%, 70%, 30%, 42%, and 21%, respectively. Figure 3 shows the preservation of ocular function. The 5-year preservation rates for ocular function in all 85 patients, the en bloc resection group, the conservative surgery group, the RADPLAT group, and the IV-CRT group were 19%, 15%, 27%, 30%, and 17%, respectively. Twenty-five of 38 patients (66%) with T4b were treated by RADPLAT or IV-CRT. In patients with T4b, there were significant differences in both overall survival and preservation of ocular function between the RADPLAT group ($n = 16$) and IV-CRT group ($n = 9$; $p = .0166$ and $p = .0173$, respectively; Figures 4 and 5).

Analyzing the clinical outcome in the en bloc resection group, there was no significant difference in the 5-year overall survival rate between patients with orbital exenteration and those without orbital exenteration (72% vs 71%; $p = .9321$; Figure 6). There was no significant difference in the 5-year local control rate between patients with orbital exenteration and those without orbital exenteration (78% vs 71%; $p = .6310$) as well. In 6 of 7

TABLE 4. Evaluation of ocular function.

	No. of patients	Ocular function				
		Removed	Nonfunctional	Functional with impairment	Functional without impairment	Unknown
En bloc resection	33	25 (76%)	0 (0%)	1 (3%)	7 (21%)	0
Conservative surgery	15	1 (7%)	2 (13%)	3 (25%)	9 (60%)	0
RADPLAT	21	1 (5%)	6 (28%)	5 (24%)	9 (43%)	0
IV-CRT	14	0 (0%)	4 (33%)	4 (33%)	4 (33%)	2
Radiation alone	4	0 (0%)	0 (0%)	1 (25%)	3 (75%)	0

Abbreviations: RADPLAT, intra-arterial chemotherapy, and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

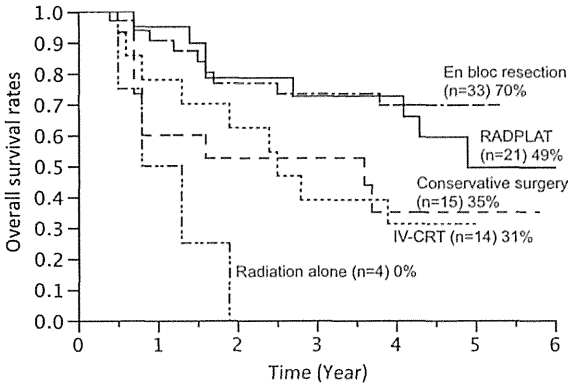

FIGURE 1. The 5-year overall survival rates for treatment modalities obtained using the Kaplan–Meier methods. RADPLAT, superselective intra-arterial chemotherapy and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

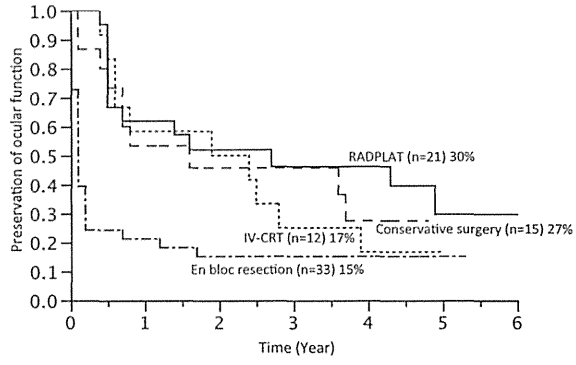

FIGURE 3. The 5-year preservation rates of ocular function for treatment modalities obtained using the Kaplan–Meier methods. RADPLAT, superselective intra-arterial chemotherapy and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

patients without orbital exenteration (86%), ocular function was evaluated as functional without impairment. Ocular function of the remaining 1 patient without orbital exenteration (14%) was evaluated as functional with impairment.

DISCUSSION

With regard to the treatment of advanced malignant maxillary sinus cancer, many authors have recommended combined therapies consisting of en bloc radical resection together with irradiation. This combined therapy has shown 5-year overall survival rates of 44% to 58%.[7–10] The 5-year overall survival rate of patients undergoing en bloc resection in our multi-institutional study was 70%, which is favorable in comparison to recent reports. One reason for the favorable results may be the improvements in surgical technique as the incidence of maxillary sinus cancer has been historically relatively high in Japan, comprising more than 1% of all malignancies and about 23% of all malignant head and neck tumors.[11] Another reason may be that the combined approach with intra-arterial chemotherapy, surgery, and radiotherapy had been gradu-

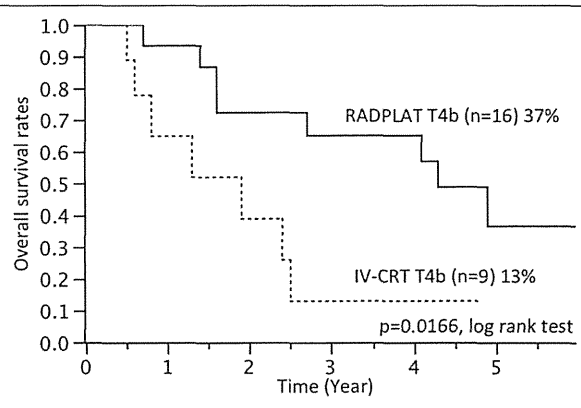

FIGURE 4. The 5-year overall survival rates for patients with T4b cancer undergoing superselective intra-arterial chemotherapy and radiotherapy (RADPLAT) or intravenous chemoradiotherapy (IV-CRT) obtained using the Kaplan–Meier methods.

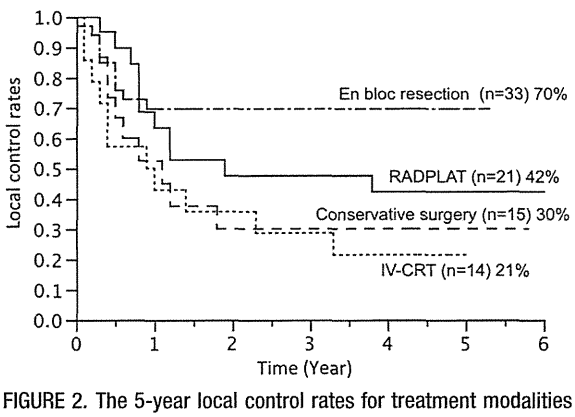

FIGURE 2. The 5-year local control rates for treatment modalities obtained using the Kaplan–Meier methods. RADPLAT, superselective intra-arterial chemotherapy and radiotherapy; IV-CRT, intravenous chemoradiotherapy.

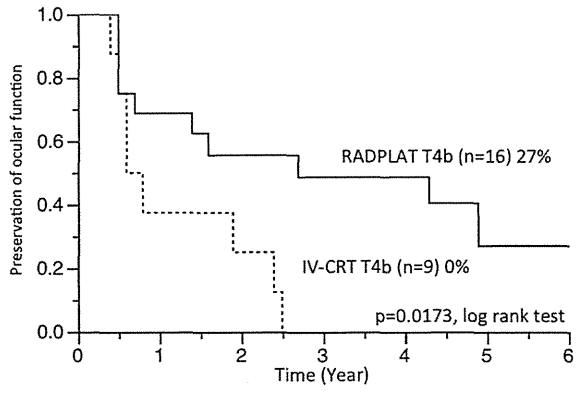

FIGURE 5. The 5-year preservation rates of ocular function for patients with T4b cancer undergoing superselective intra-arterial chemotherapy and radiotherapy (RADPLAT) or intravenous chemoradiotherapy (IV-CRT) obtained using the Kaplan–Meier methods.

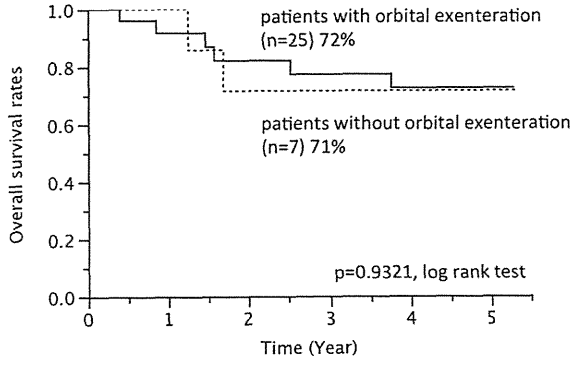

FIGURE 6. The 5-year overall survival rates for patients undergoing en bloc resection with orbital exenteration and those undergoing en bloc resection without orbital exenteration obtained using the Kaplan–Meier methods.

ally developing for patients with maxillary sinus cancer since the 1950s in Japan.[12,13]

Homma et al[5] reported that RADPLAT consisting of targeting superselective intra-arterial chemotherapy and concurrent radiotherapy was performed for patients with T3 to T4 nasal and paranasal sinus cancer. The 5-year overall survival rate was reported to be 69.3%. This nonsurgical treatment is expected to preserve the orbital contents and to avoid cosmetic problems for patients with advanced maxillary sinus cancer.

In this multi-institutional study, survival rates and ocular function were evaluated among various treatment modalities. However, we recognized that our study was limited by its retrospective nature, which resulted in a bias toward treatment selection. T4b maxillary sinus cancer is generally considered unresectable. Therefore, most of the patients with T4b maxillary sinus cancer were not treated by en bloc resection. It is probably inappropriate to compare overall survival rates among treatment modalities because of this inequality. Therefore, we analyzed the overall survival rates and ocular function–preservation rates between patients with T4b cancer treated by RADPLAT or IV-CRT, and noticed that both the overall survival rate and ocular function–preservation rate in the RADPLAT group were significantly higher than those in the IV-CRT group. A randomized phase 3 trial in The Netherlands indicated that RADPLAT was not superior to cisplatin-based IV-CRT for advanced head and neck cancer in terms of locoregional control and survival.[14] However, it was reported in this literature that there were significantly higher local and locoregional rates and disease-free survival with RADPLAT for large (>30 mL) lateralized tumors. Advanced maxillary sinus cancers are generally large and lateralized, do not extend beyond the midline, and have simple artery feeding that is easy to access. Therefore, we believe that RADPLAT has an advantage over IV-CRT in the control of massive primary tumors for patients with advanced maxillary sinus cancer.

In terms of surgical treatment, it was reported that sparing of the orbital soft tissue during en bloc resection did not reduce the rate of cure or local control when the periorbita had not been transgressed.[1] In addition, Imola and Schramm[2] suggested that eye preservation could be attempted in paranasal sinus cancers that invaded the orbital soft tissues with penetration through the periorbita, and overall eye function was reported as functional without impairment in 54%, functional with impairment in 37%, and nonfunctional in 9% for patients in whom orbital contents had been preserved. On the other hand, Dulguerov et al[15] suggested that the role of orbital exenteration was significant in cases with orbital invasion. It was reported that the locoregional control rate in patients with orbital exenteration was higher than that in patients without orbital exenteration (79% vs 14%, respectively; $p = .03$).

Our results indicated that the overall survival rate of patients without orbital exenteration were comparable to that of patients with orbital exenteration. Therefore, it was considered that preserving orbital contents was applied adequately in this multi-institutional study. Furthermore, ocular function was evaluated as functional without impairment in 86% of patients without orbital exenteration. These favorable data support selective orbital preservation. However, we need further study to determine the indication of orbital preservation during en bloc resection, and we cannot ignore the role of adjunctive treatment for patients without orbital exenteration. On the other hand, our results showed that 76% of patients undergoing en bloc resection needed orbital exenteration and this had significant cosmetic problems. It is probably difficult to spare the orbit when en bloc resection is applied to patients with maxillary sinus cancer with orbital invasion.

In conclusion, the overall survival rate of the en bloc resection group was favorable, and preservation of orbital contents did not reduce the survival rate for patients undergoing en bloc resection. However, it may be difficult to preserve orbital contents during en bloc resection as we found that 76% of the en bloc resection group underwent orbital exenteration in our study. In addition, it is thought that RADPLAT has higher oncologic efficacy than IV-CRT against T4b maxillary sinus cancer.

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HEAD AND NECK

Early and long-term morbidity after minimally invasive total laryngo-pharyngo-esophagectomy with gastric pull-up reconstruction via thoracoscopy, laparoscopy and cervical incision

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Abstract Total laryngo-pharyngo-esophagectomy (TLPE) with gastric pull-up reconstruction is still considered to be associated with major complications and a significant risk of in-hospital death. Minimally invasive esophagectomy, avoiding thoracotomy and laparotomy, has been increasingly performed for esophageal malignancies with the hope of reducing mortality and morbidity, such as pulmonary complications. The aim in this study was to assess early and long-term morbidity as well as treatment outcomes in patients treated with TLPE with gastric pull-up reconstruction via thoracoscopy, laparoscopy and cervical incision. From 2004 to 2013, 10 patients with a median age of 64 years (range 47–71 years) underwent minimally invasive TPLE with gastric pull-up reconstruction. Seven of the 10 patients had previously received radiotherapy. As for early postoperative complications, no patient died during the early postoperative period, and pneumonia was observed in 1, skin necrosis in 1, pseudomembranous enterocolitis in 1, arrhythmia in 2, hemorrhage in the neck in 2, anastomotic leakage in the neck in 3, and tracheal necrosis in 6 patients. Three patients developed tracheostomal stenosis as a long-term postoperative complication, and an anastomotic stricture was observed in one patient. All patients were able to achieve oral intake, but 3 patients required feeding tube support. In conclusion, postoperative systemic complications during the early postoperative period were considered to be acceptable, although wound complications such as tracheal necrosis and anastomotic leakage were commonly observed. Therefore, this minimally invasive procedure might help reduce mortality and morbidity in patients requiring TLPE with gastric pull-up reconstruction.

Keywords Cervical esophageal cancer · Hypopharyngeal cancer · Postoperative complication · Minimally invasive esophagectomy

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Introduction

Total laryngo-pharyngo-esophagectomy (TLPE) together with gastric pull-up reconstruction, which involves surgery to a wide area including the neck, chest and abdomen, remains a major surgical challenge. Recently, minimally invasive esophagectomy (MIE), which avoids the need for thoracotomy and laparotomy, has been increasingly performed for esophageal malignancies in the hope of reducing mortality and morbidity, such as pulmonary complications [1, 2]. Several studies have reported on the complications and survival in patients undergoing TLPE together with gastric pull-up reconstruction [3–6]. However, these reports did not mention whether the esophagectomy was performed via an open or endoscopic approach. Based on the period in which the treatments were performed, we speculate that the surgery proceeded via a transhiatal or transthoracic esophagectomy with laparotomy. Further, there have been no reports of TPLE with

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gastric pull-up being performed both thoracoscopically and laparoscopically in a group of patients. At our institute, we have been performing this procedure for over 10 years and, therefore, we have been able to assess the early and long-term morbidity as well as treatment outcomes in patients undergoing TLPE with gastric pull-up reconstruction via thoracoscopy, laparoscopy and cervical incision.

Patients and methods

Between 2004 and 2013, ten patients underwent TLPE with gastric pull-up reconstruction via thoracoscopy, laparoscopy and cervical incision for double cancers of the hypopharynx and thoracic esophagus ($n = 2$), cervical esophageal cancer ($n = 5$), or hypopharyngeal cancer with esophageal extension ($n = 3$) (Table 1). Patients consisted of 8 males and 2 females, with a median age of 64 years (range 47–71 years). One patient received total laryngectomy due to laryngeal cancer prior to the development of hypopharyngeal cancer. Seven patients had previously received radiotherapy, with five of the seven patients receiving radiotherapy with or without chemotherapy for hypopharyngeal or cervical esophageal cancer, and two receiving postoperative radiotherapy for laryngeal cancer or oral cavity cancer. All of the cancers mentioned above were squamous cell carcinomas.

Three patients were unable to obtain adequate oral intake prior to surgery due to esophageal stenosis resulting from esophageal cancer ($n = 2$) or chemoradiotherapy ($n = 1$). In addition, one patient, who previously underwent total laryngectomy with bilateral neck dissection and postoperative radiotherapy, was unable to obtain oral intake due to a pharyngo-cutaneous fistula resulting from the previous surgery ($n = 1$). This patient had undergone hypopharyngectomy due to hypopharyngeal cancer, resulting in a circumferential pharyngeal defect. A free jejunum transfer could not be indicated as there were no vessels with which to anastomose with vessels of a free jejunal flap in the neck due to the prior surgery and radiotherapy. Therefore, the pharynx was reconstructed using a pectoral major musculocutaneous flap; however, this resulted in anastomotic leakage and prevented oral intake. The remaining 6 patients were able to obtain adequate oral intake, but 3 of them required opioids for pain on swallowing. One patient received a tracheostomy due to airway compromise.

All 10 patients underwent reconstruction by gastric pull-up, and a free jejunal flap was also used in 1 patient. The grafts used were whole stomach ($n = 2$), subtotal gastric tube ($n = 5$), slender gastric tube ($n = 1$), elongated stomach roll ($n = 1$), and stomach roll with free jejunal flap ($n = 1$), and the grafts were passed through the posterior mediastinum ($n = 8$), retrosternum ($n = 1$), or antesternum ($n = 1$). One patient (case 4) underwent reconstruction by gastric pull-up and a free jejunal flap as the stomach roll did not reach the stump of the pharynx. Although the design of the grafts and routes through which they passed were decided on the basis of the specific characteristics of each case and the surgeons' discretion, grafts were generally constructed from the subtotal gastric tube and passed through the posterior mediastinum. At least one lobe of the thyroid gland was left in contact with the trachea to avoid tracheal necrosis in 7 patients.

Postoperative complications, such as tracheal necrosis, skin necrosis, anastomotic leakage and hemorrhage, were divided into severe and mild groups. The severe groups included patients who required additional surgery in an operating room and those who required more than 1 month to recover. The mild groups consisted of patients to whom the above criteria did not apply. Complications were categorized as early ($\leq$30 days postoperatively) or late (>30 days postoperatively).

Results

As for early postoperative complications, no patient died during the early postoperative period, and pneumonia was observed in 1, arrhythmia in 2, anastomotic leakage in the neck in 3, tracheal necrosis in 6, and hemorrhage (severe) in the neck in 2 patients (Table 2). Two patients who experienced bleeding developed severe anastomotic leakage. One of the two experienced bleeding from the external carotid artery; however, his fistula closed spontaneously thereafter. The other patient experienced bleeding from the stump of the pharynx due to an infection in the surrounding tissue resulting from anastomotic leakage, and the pharynx was reconstructed using a pectoral major musculocutaneous flap. One patient who suffered from crust formation on his trachea 3 cm inferiorly from the tracheostoma for more than 2 months was among the 6 patients who developed tracheal necrosis. The five other patients who developed tracheal necrosis near the tracheostoma but involving an area of less than 1 cm needed only debridement. Skin necrosis (mild) and pseudomembranous enterocolitis were observed in one patient each in the early postoperative period. Three patients developed tracheostomal stenosis as a long-term postoperative complication and anastomotic stricture was also observed in one patient. All patients were able to achieve oral intake, although 3 patients required feeding tube support.

The follow-up period after surgery for surviving patients ranged from 8 to 23 months (median, 22 months). The 3-year overall survival rate, calculated by the Kaplan–Meier method, was 64.3 % (Fig. 1). Two patients died of

Table 1 Patient characteristics, treatment, and outcome

No.	Age/sex	Site/cStage	RT	Oral intake (pre-op)	Opioid use	Tracheostomy	Thyroid left in contact with trachea	Reconstruction route	Postoperative complications	Oral intake (post-op)	Outcome follow-up period (months)
1	58/M	Hypopharynx T3N2bM0 thoracic esophagus T1bN0M0	No	Yes	Yes	No	Left	Elongated stomach roll mediastinum	Tracheal necrosis (mild)	Yes (+tube sup)	Dead 47
2	68/F	Esophagus (Ce) T3N0M0	No	No	No	No	None	Slender gastric tube retrosternum	Arrhythmia, tracheostomal stenosis	Yes (+tube sup)	Alive 22
3	47/M	Hypopharynx T4aN2bM0 + esophageal extension	Yes	Yes	Yes	No	Both	Whole stomach mediastinum	Anastomotic leakage (severe), hemorrhage (severe)	Yes	Dead 17
4	70/F	Esophagus (Ce) T4N1M1	Yes	No	No	Yes	Left	Subtotal gastric tube + free jejunum antesternum	Pneumonia, skin necrosis in the neck (mild), tracheal necrosis (mild), tracheostomal stenosis	Yes	Dead 46 (lung ca)
5	61/M	Esophagus (Ce) T4N1M0	Yes	Yes	No	No	None	Subtotal gastric tube mediastinum	Tracheal necrosis (mild)	Yes	Dead 17 (lung ca)
6	69/M	Esophagus (Ce) T4bN2M0	Yes	No	No	No	Right	Subtotal gastric tube mediastinum	Tracheal necrosis (severe), tracheostomal stenosis	Yes	Dead 3 (unknown)
7	57/M	Hypopharynx T1N2bM0 + esophageal extension (at recurrence)	Yes	Yes	No	No	Both	Subtotal gastric tube mediastinum	Arrhythmia, tracheal necrosis (mild)	Yes	Alive 25
8	59/M	Esophagus (Ce) T3N1M0	Yes (for oral cavity ca)	Yes	Yes	No	None	Subtotal gastric tube mediastinum	Hemorrhage (severe), gastric tube necrosis, anastomotic leakage (severe)	Yes	Alive 20
9	71/M	Hypopharynx T4N0M0 + esophageal extension	Yes (for laryngeal ca)	No	No	Yes (TL)	Right	Whole stomach mediastinum	Anastomotic leakage (mild), anastomotic stricture	Yes (+tube sup)	Alive 15
10	70/M	Hypopharynx T2N0M0 + thoracic esophagus T2N0M0	No	Yes	No	No	Left	Subtotal gastric tube mediastinum	Pseudomembranous enterocolitis	Yes	Alive 11(lumg meta)

Ce cervical, *tube sup* feeding tube support, *TL* total laryngectomy

Table 2 Postoperative complications

Complication	*n*
Early	
Tracheal necrosis	6
Mild	5
Severe	1
Anastomotic leakage	3
Mild	1
Severe	2
Arrhythmia	2
Hemorrhage (severe)	2
Pneumonia	1
Skin necrosis in the neck (mild)	1
Pseudomembranous enterocolitis	1
Late	
Tracheostomal stenosis	3
Anastomotic stricture	1

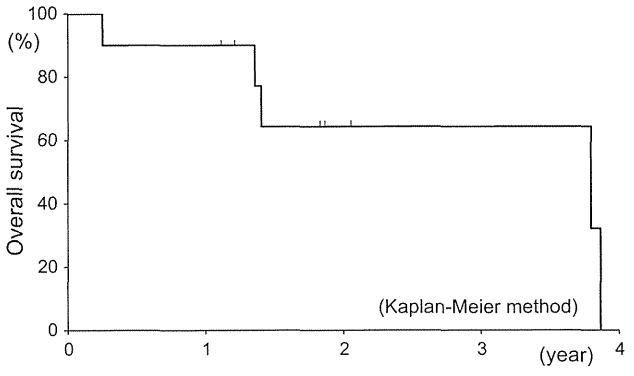

Fig. 1 Overall survival curve

neck recurrence and distant metastasis without primary site recurrence, one patient died of an unknown cause, and 2 patients died of lung cancer. The lung cancers in these patients were confirmed pathologically not to have metastasized from either the previous head and neck or esophageal cancer. Five patients currently remain alive without disease, except for one patient with lung metastasis. No patient received a tracheo-esophageal shunt, and all of them communicate using an electrolarynx or through writing.

Discussion

Carcinoma of the cervical esophagus has a poor prognosis, with 3- and 5-year survival rates reported to range from 18 to 35.4 % and from 12 to 33 %, respectively [7]. Similarly, hypopharyngeal cancer with esophageal extension also has a poor prognosis, and is staged as T4. Recent progress with concurrent chemoradiotherapy (CCRT) for patients with locally advanced head and neck or thoracic esophageal cancer has motivated many physicians to treat cervical esophageal cancer with initial CCRT. For most patients with cervical esophageal cancer, radical surgery has mandated simultaneous total laryngectomy. Therefore, most patients with cervical esophageal cancer prefer CCRT to surgery due to the potential for laryngeal preservation [8]. In reality, however, not a few patients have experienced a residual or recurrent tumor after CCRT. Even if the tumor is successfully controlled by CCRT, pharyngeal or esophageal stricture can be a late complication at the tumor site [9] as the postcricoid area and cervical esophagus are anatomically narrow. Surgery is often indicated after CCRT for such patients, while for patients with previously irradiated hypopharyngeal, cervical esophageal or other head and neck cancer, surgery is the only curative option. Therefore, we focused on total laryngo-pharyngo-esophagectomy (TLPE) with gastric pull-up reconstruction for such patients.

Minimally invasive esophagectomy (MIE) has been introduced with the hope of reducing mortality and postoperative systemic complications, such as pulmonary infection. A prospective randomized controlled trial for patients with resectable cancer of the esophagus or gastroesophageal junction was performed to compare open esophagectomy ($n = 56$) and MIE ($n = 59$) [1]. Sixteen patients (29 %) in the open esophagectomy group developed pulmonary infection in the first 2 weeks compared with 5 (9 %) in the MIE group ($p = 0.005$). The authors concluded that this finding provides evidence for the short-term benefits of MIE for patients with resectable esophageal cancer. Additionally, MIE preserved quality of life (QOL) better than did open esophagectomy, with QOL measurements taken 6 weeks after surgery better for patients in the MIE group than for those in the open esophagectomy group. QOL measurements were not performed in this study, but we felt the early postoperative status of the patients included in this study was better than that in the early period of patients in the open surgery group in our institution, although no QOL data were obtained for that group either.

As for postoperative complications after TLPE with gastric pull-up reconstruction, the in-hospital mortality rate was previously reported to be 0–16 % [4–6, 10]. In this study, no patient died during the early postoperative period, although one patient died at home 3 months after surgery due to an unknown cause. As for postoperative pulmonary infection after TLPE, it was previously reported to be 10–26 % [5, 6, 10]. We found that 1 out of 10 patients (10 %) in this study had pneumonia in the early postoperative period, although 9 out of 10 patients

received mediastinal dissection simultaneously. This rate was thought to be low in comparison to the figures for post-TLPE complications reported previously and we considered that this was due to MIS. Early postoperative complications were reported in detail by Shuangba et al. [6] who reported the outcomes for 208 patients after TLPE with gastric pull-up reconstruction. With regard to early postoperative thoraco-abdominal complications, pneumonitis was observed in 23 (11.1 %), pleural effusion in 15 (7.2 %), chylous fistula in 4 (1.9 %), heart failure in 4 (1.9 %), hemoperitoneum in 2 (1 %), and burst abdomen in 2 patients (1 %). In this study, the only thoraco-abdominal complications observed involved arrhythmia in 2 patients (20 %) and pneumonia in 1 patient (10 %). It was difficult to compare the two studies, but the results of our study appear to be roughly comparable to Shuangbas' report.

Tracheal necrosis and anastomotic leakage most commonly appeared in the early postoperative period. We consider tracheal necrosis to be one of the most frequent and difficult problems to resolve. The cervical trachea receives its blood supply primarily from branches of the inferior thyroid artery, and the lower cervical trachea is supplied from the tracheoesophageal branch of the subclavian artery [11]. The superior thyroid artery does not extend any direct branches to the trachea. However, it is anastomosed with the inferior thyroid artery in and around the thyroid gland. The extreme distal thoracic trachea is always supplied by the bronchial artery. The rest of the blood supply is derived from the innominate-subclavian system. Thorough bilateral paratracheal dissection usually results in the sacrifice of the bilateral inferior thyroid arteries, although we try to leave the thyroid gland in contact with the trachea where possible. However, in this study, we found that 5 patients developed mild tracheal necrosis, so maintaining contact between the thyroid gland and the trachea was not sufficient to prevent tracheal necrosis. In patients with hypopharyngeal and esophageal cancer, thorough paratracheal dissection should be performed. Although preservation of the blood supply to trachea from the inferior thyroid arteries results in incomplete dissection and might increase the risk of recurrence, it is preferable to preserve the blood supply to trachea from the inferior thyroid arteries. Therefore, the question of whether or not to preserve the blood supply to the trachea from the inferior thyroid arteries depends on the specific conditions in each individual case. Further, although the trachea is usually freed from the aorta by preserving the left bronchial arteries, the right bronchial artery is sacrificed during the esophagectomy. We now consider that recent progress in endoscopic surgery enables us to preserve the right bronchial artery. We expect that this will aid in preventing tracheal necrosis in future.

Anastomotic leakage developed in 3 patients who previously underwent irradiation. We speculate that this was due to the lack of blood supply to the graft and to delays in wound healing after the previous radiotherapy. The reason for the lack of blood supply to the graft was considered to involve the design, length and route of the graft. Stress on the suture lines also led to a lack of blood supply to the graft and anastomotic leakage. Reconstruction by gastric pull-up and free jejunal transfer might be one answer to these problems. We speculate that it would enable reconstruction with less stress, and might provide better blood supply to gastric grafts as well as aid in preventing anastomotic leakage.

Surgery following radiotherapy remains a technical challenge. In this series, 7 of the 10 patients had received previous radiotherapy. As a result, severe postoperative complications developed in 3 patients of 7 previously irradiated patients. However, they were all manageable and no patients died in the early postoperative period, partly because this surgical procedure is relatively simple in terms of both the surgical resection and reconstruction. Therefore, while the surgery is still considered a procedure associated with major complications, complications involving the wound were relatively mild due to the fact that there were no dead spaces or anastomosis in the thorax as the gastric tube, which is larger than the esophagus, filled the thoracic defect and the suture line in this procedure was located in the neck area. These aspects are speculated to aid in minimizing morbidity while limiting complications.

As for treatment outcome, only 2 patients died of disease. Both patients had neck lymph node and distant metastasis. No patient developed primary site recurrence as this procedure removes the pharynx as well as the whole esophagus with surgical margins sufficient for primary site resection. In addition, no patient developed recurrence in the mediastinum. Based on this result, the procedure involving the mediastinum was considered to be performed appropriately. Two patients also died of lung cancer, and 2 patients had other head and neck cancers before surgery. Further, 2 patients received TLPE due to double cancers of the hypopharynx and thoracic esophagus. Therefore, a total of 6 patients had more than one cancer in the upper aerodigestive tract. All of them had histories of smoking and alcohol consumption, which is a problem that concerns every head and neck cancer patient. However, although follow-up period was short, 4 patients currently remain alive without disease despite such patients generally having a poor prognosis. To be honest, the postoperative quality of life of these patients is poor, with patients not being able to speak and all of them suffering from postgastrectomy syndrome and other sequelae. However, we would like to stress that while the 4 patients did not have oral intake

preoperatively, all achieved oral intake after surgery. If patients cannot or will not swallow due to the presence of a tumor, this procedure is worthwhile.

In conclusion, no patient died during the early postoperative period and postoperative systemic complications such as pneumonia were considered to be equal to or less than other reports, although postoperative wound complications such as tracheal necrosis and anastomotic leakage were commonly observed in the early postoperative period. Further, to clarify the benefits of this procedure, QOL measurements are required in the early postoperative period. TLPE with gastric pull-up reconstruction is still considered a procedure associated with major complications and a significant risk of in-hospital death, but this minimally invasive procedure might help reduce mortality and morbidity in patients requiring TLPE with gastric pull-up reconstruction.

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Management for squamous cell carcinoma of the nasal cavity and ethmoid sinus: A single institution experience

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ABSTRACT

Objective: Here we report our experience of patients with squamous cell carcinoma (SCC) of the nasal cavity and ethmoid sinus (NC&ES) together with an analysis of treatment outcomes.
Methods: A retrospective analysis was performed using data from 25 consecutive patients treated between 2000 and 2012. Four patients were diagnosed with T1, 3 with T2, 4 with T3, 7 with T4a, and 7 with T4b disease. No patient had lymph node metastasis.
Results: Twelve patients were treated with surgery with/without radiotherapy and with/without chemotherapy. Of these, 4 underwent endoscopic surgery without an open approach and 3 required an anterior skull base approach. Thirteen were treated with radiotherapy; 1 with radiotherapy alone, and 4 and 8 with intravenous and intra-arterial chemotherapy, respectively. The 5-yr overall survival for T1–3, T4a, and T4b disease was 53.9%, 71.4%, and 29.0%, respectively. The 5-yr disease-specific survival for T1–3, T4a, and T4b disease was 74.1%, 71.4%, and 29.0%, respectively.
Conclusion: Our treatment policy for patients with SCC of NC&ES, which basically follows the NCCN guideline, was considered to be appropriate. However, several points in terms of surgery and non-surgical approach remain to be solved through further research.

1. Introduction

Malignant tumors of the nasal cavity and ethmoid sinus (NC&ES) are rare neoplasms that constitute approximately 35% of all malignancies of the paranasal sinuses and nasal cavity in Japan [1], although lower rates are reported in Western countries. NC&ES fall into the same category of anatomic site and their stages are determined using the same criteria in the UICC classification.

The number of patients with malignant tumors of NC&ES treated at a single center is small. Therefore, some reports have included patients from several decades ago, and the time factor must have influence on pretreatment diagnosis and treatment outcome. Indeed, the application of endonasal endoscopic resection of NC&ES tumors has been increasing, and induction chemotherapy and concomitant chemoradiotherapy have been developed for head and neck cancers in recent times. In addition, there are many histological types of malignant tumors that develop in the paranasal sinuses and nasal cavity, such as squamous cell carcinoma (SCC), adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, olfactory neuroblastoma, malignant melanoma, undifferentiated carcinoma, and so on. Therefore, there is a scarcity of prospectively collected data on the management options and outcomes because of the rarity of this disease [2]. The retrospective data collected to date also include data for different sites, such as the maxillary sinus, which accounts for over 50% of sinonasal malignancies, as well as data for many histological types. Therefore, it is difficult to know how to treat patients with tumors in a specific site and with a specific histology. In this study, we focused on SCC of the NC&ES, which is one of the major histological types of NC&ES.

The purpose of the present study was to report our experience with 25 consecutive patients with SCC of the NC&ES after 2000, with an analysis of treatment outcomes.

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2. Materials and methods

A retrospective analysis was performed on data from 25 consecutive patients with previously untreated SCC of NC&ES treated between January 2000 and December 2012 in Hokkaido University Hospital. One patient was excluded because he was treated with palliative intent due to his poor medical condition.

All patients were initially evaluated by a multidisciplinary team consisting of head and neck surgeons and radiation oncologists, and tumors were classified according to the 7th Edition of the Union for International Cancer Control (UICC) staging system published in 2009. Patients visiting our hospital before 2009 were restaged according to the UICC 7th edition. The stage of the tumor was determined on the basis of patient history, physical examination, chest X-rays, as well as computed tomography (CT) and/or magnetic resonance imaging (MRI). Approval for this study was obtained from the Institutional Review Board at Hokkaido University.

2.1. Treatment strategies

All cases were discussed by a multidisciplinary tumor board. All 25 patients were treated with curative intent. In accord with our institutional policy, limited disease (T1–2 N0) was treated by surgery or radiotherapy alone. Radiotherapy was recommended if adverse features, such as positive or close margins, were confirmed pathologically. Locally advanced and resectable disease was treated by a combination of surgery followed by adjuvant radiotherapy or radiotherapy with intravenous (IV) or intra-arterial (IA) chemotherapy, and unresectable tumors were treated by radiotherapy with chemotherapy (IV or IA).

2.2. Statistical analysis

All patients were closely observed during the follow-up period, with the median follow-up period for surviving patients ranging from 1.5 to 14 years (median, 8.3 years).

In this study, the detailed anatomical sites in which the primary tumor developed were evaluated using CT and MR imaging. The primary tumor extension sites were classified according to the 7th UICC staging system and included the medial wall or floor of the orbit, maxillary sinus, palate, cribriform plate, anterior orbital contents, skin of the nose or cheek, minimal extension to the anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses, orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, and clivus.

The probability of overall survival was computed from the beginning of treatment to the time of death from any cause or the date of the last follow-up contact for surviving patients, and the probability of disease-specific survival was computed to death from disease or the date of last follow-up contact for surviving patients. They were calculated by the Kaplan–Meier method and compared using the log-rank test. Two-sided P values <0.05 were considered statistically significant. A prognostic analysis was performed to study the following variables: age, sex, and extension to the primary tumor extension sites. Statistical analysis was performed using JMP Pro 11.0.0 statistical software (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Twenty-five patients were enrolled in this study. Patients consisted of 17 males and 8 females, with a median age of 65 years (range 25–81 years). Thirteen patients (52%) had tumors arising in the ethmoid sinus, and 12 (48%) in the nasal cavity. Four patients (16%) was diagnosed with T1, 3 (12%) with T2, 4 (16%) with T3, 7 (28%) with T4a, and 7 (28%) with T4b disease. No lymph node involvement was noted in any patients (Table 1). Inverted papillomas were found in surgical or biopsy specimens from 4 patients.

3.2. Treatment modalities

Treatment according to T stage is shown in Table 2. Twelve patients (48%) were treated with surgery. Of these, 4 (16%) were treated with surgery alone, 6 (24%) with surgery and postoperative radiotherapy, and 2 (8%) with induction chemotherapy, surgery, and postoperative radiotherapy. Thirteen patients (52%) underwent radiotherapy without surgery. Of these, one patient (4%) was treated with radiotherapy alone. Radiotherapy and concomitant intravenous chemotherapy (IV-CRT) were undertaken for 4 (16%), and 2 (8%) patients also received induction chemotherapy. Eight patients (32%) were treated with radiotherapy and concomitant intra-arterial chemotherapy (RADPLAT). The treatment protocol for IV-CRT and RADPLAT has been described elsewhere [3–6]. To summarize, RADPLAT consisted of super-selective intra-arterial infusions of cisplatin (100–120 mg/m^2/week, 4 times) with simultaneous intravenous infusions of thiosulfate to neutralize cisplatin toxicity and conventional radiotherapy (65–70 Gy). IV-CRT consisted of weekly cisplatin (40 mg/m^2) or carboplatin (AUC 1.5) together with radiotherapy (70 Gy) over 7 weeks. Induction chemotherapy consisted of a combination of cisplatin, docetaxel, and 5-fluorouracil or of nedaplatin, docetaxel, and 5-fluorouracil.

Surgical approach according to T stage is shown in Table 3. Of the 12 patients who underwent surgery, 4 patients received endonasal endoscopic surgery without an open approach. A further two patients underwent tumor resection via a nasal-alar sulcus incision and endonasal endoscopy to achieve a good view of the tumor and allow resection with an adequate margin as the tumors were located tangential to the external nares. One patient underwent tumor resection by a gingivobuccal approach with endoscopy. Two patients also underwent resection via lateral rhinotomy. All 9 of these patients presented with limited disease (T1–3) of the NC&ES. The remaining 3 patients with T4 disease were treated via an anterior skull base approach with an endonasal endoscopic approach and with/without a lateral rhinotomy approach. Reconstruction of the surgical defect of the anterior skull base using a pericranial flap was required in all 3 patients. The

Table 1
Patient characteristics ($n=25$).

	Number of patients
Age	
Range	25–81
Median	65
Average	61.8
Gender	
Male	17
Female	8
Primary tumor site	
Nasal cavity	12
Ethmoid sinus	13
T stage	
1	4
2	3
3	4
4a	7
4b	7
N stage	
0	25

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Table 2
Treatment according to T stage ($n = 25$).

T (n)	Treatment	n	Outcome
T1 (4)	Surg	2	2:NED
	Surg, RT	1	2:NED
	RT	1	1:DOD(P)
T2 (3)	Surg, RT	2	2:DOC
	Surg	1	1:NED
T3 (4)	Surg, RT	1	1:NED
	CT, Surg, RT	1	1:NED
	Surg	1	1:DOD(P)
	RADPLAT	1	1:NED
T4a (7)	Surg, RT	1	1:NED
	CT, Surg, RT	1	1:DOD(D)
	CRT	1	1:DOD(P)
	RADPLAT	4	4:NED
T4b (7)	Surg, RT	1	1:DOD(P)
	CRT	1	1:DOD(P)
	CT, CRT	2	1:NED, 1:DOD(P)
	RADPLAT	3	1:NED, 1:DOD(P), 1:DOD(D)

Abbreviations: Surg, surgery; RT, radiotherapy; CT, chemotherapy; RADPLAT, radiotherapy with intra-arterial chemotherapy; IV-CRT, radiotherapy with intravenous chemotherapy; NED, no evidence of disease; DOD, dead of disease; DOC, dead of other cause; P, primary disease; D, distant disease.

remaining 9 patients did not need reconstruction, and the postoperative course was uneventful in all 9 patients.

3.3. Overall survival and disease-specific survival rates

The 5-year overall survival and disease-specific survival rate calculated by the Kaplan–Meier method, was 52.3% and 59.9%, respectively (Fig. 1). Seven patients died of primary site recurrence and 2 patients of distant metastasis without primary site recurrence. Two patients with T2 tumor died of other causes. The 5-yr overall survival for T1–3, T4a, and T4b disease was 53.9%, 71.4%, and 29.0%, respectively. The 5-yr disease-specific survival for T1–3, T4a, and T4b disease was 74.1%, 71.4%, and 29.0%, respectively (Fig. 2). Patients with T4b had a worse disease-specific survival rate than did those with T1–3 ($P = 0.0413$).

Table 3
Surgical approach according to T stage ($n = 12$).

	T1–2	T3	T4	Total
EE	3	1		4
EE + GB		1		1
EE + NAS	2			2
EE + SB			2	2
EE + SB + LR			1	1
LR	1	1		2
Total	6	3	3	12

Abbreviations: EE, endoscopic endonasal approach; GB, gingivobuccal approach; NAS, nasal-alar sulcus incision; SB, skull base approach; LR, lateral rhinotomy.

Univariate Cox proportional hazard analysis revealed that the medial wall or floor of the orbit extension, pterygoid plate extension, and orbital apex extension were factors for OS (Table 4). However, they were not found to be independent factors for OS in the multivariate analysis. Age, sex, and extension to other anatomical sites were not factors for OS in the univariate analysis.

4. Discussion

SCC is aggressive cancer, so surgery, by means of en bloc resection, was traditionally regarded as the ideal form of intervention. However, transoral resection has been becoming more popular for head and neck cancer, especially for oropharyngeal and laryngeal caner. Hinni et al. concluded that piecemeal removal of tumors with three-dimensional margin mapping using an operating microscope or rod telescope is safe from an oncologic standpoint, and reduces morbidity and length of hospital stay [7,8].

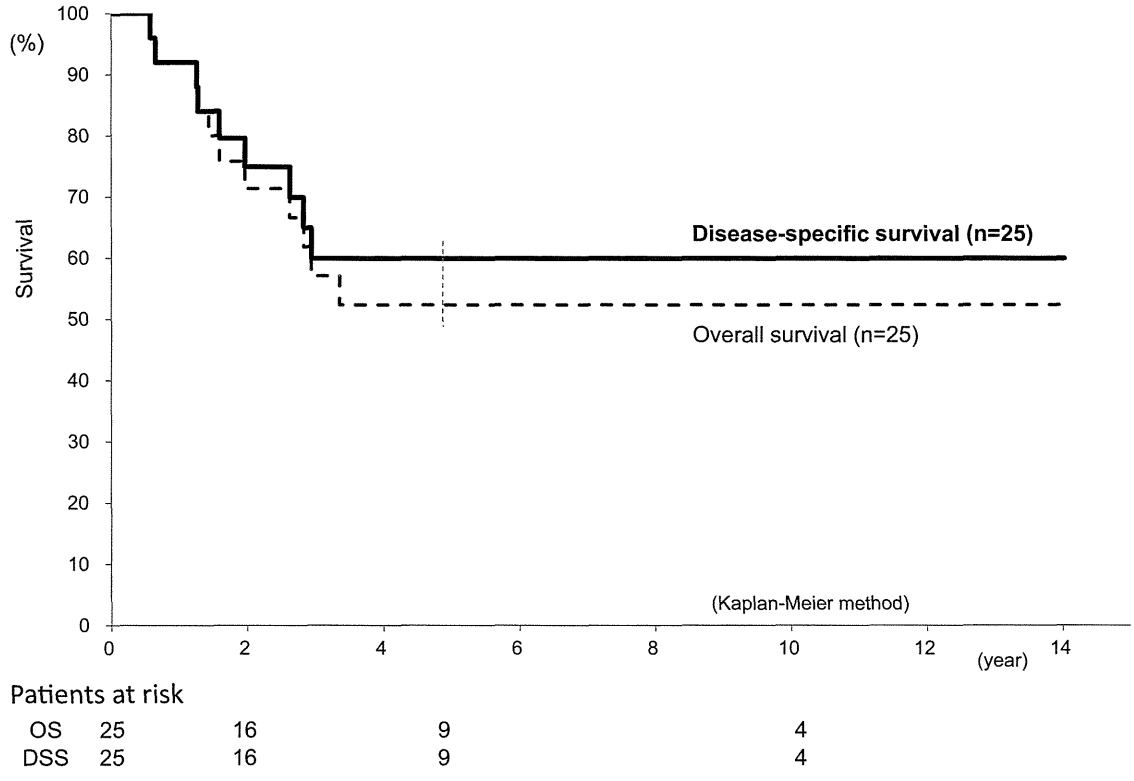

Fig. 1. Overall survival and disease-free survival rate for all patients ($n = 25$).

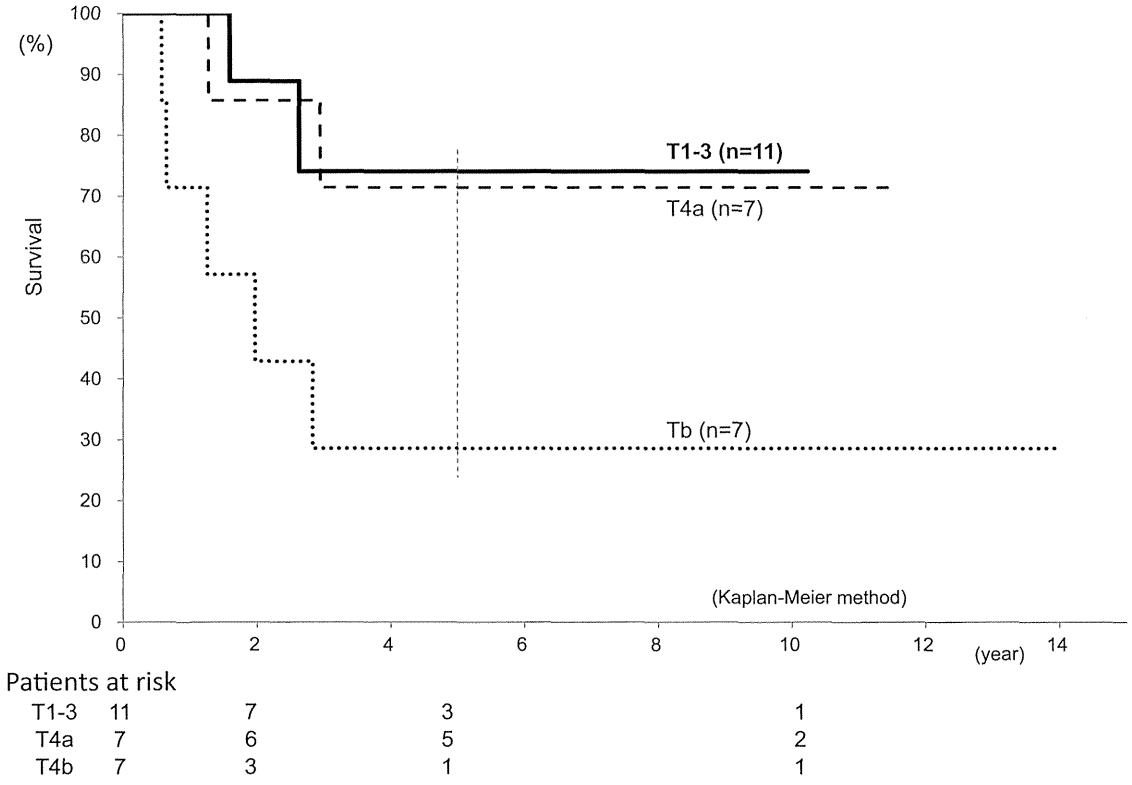

Fig. 2. Disease-specific survival rate according to T classification.

As for cancer of the NC&ES, en bloc resection is not often achieved even by lateral rhinotomy and/or an anterior skull base approach, and usually requires debulking or segmental resection. In addition, in large tumors such as T4 NC&ES, optimum visualization cannot necessarily be achieved without endoscopic assistance when trying to en bloc resection, even by an open approach. Further, recent advances in endoscopic instruments have allowed multi-angled and magnified views of the tumor limits, facilitating tumor resection [9]. Therefore, several patients who underwent surgery through an open approach early in this study might have undergone an endonasal endoscopic approach if treated more recently. Under these circumstances, we should no longer stick with en bloc resection, but should seek to achieve negative margins with a good view regardless of whether an open or endonasal endoscopic approach is used.

Reconstruction of skull base defects has become controversial since an endonasal endoscopic approach was introduced for the treatment of skull base tumors, as patients with locally advanced SCC of NC&ES usually require postoperative radiotherapy and secure cranionasal separation is necessary to prevent postoperative complications such as cerebrospinal fluid leakage and meningitis. Postoperative complications often result in delays in the commencement of postoperative radiation therapy. In addition, the flap which separates the cranial cavity from the sinonasal tract has to be strong enough to tolerate postoperative radiotherapy. For this reason, a vascularized pericranial flap is more reliable than free grafting. Pedicled flaps using the mucosa of the nasal cavity, such as a Hadad-Bassagasteguy flap and pedicled inferior turbinate flap, are available for use with modestly sized tumors and are a suitable option for cases with minimal skull base defects. However, in locally advanced SCCs of NC&ES, the mucosa used in the formation of such flaps is often removed with the cancer. And in large defects of the skull base, larger flaps are needed. In such situations, a pericranial flap is suitable. Indeed, 3 patients who underwent anterior skull base resection, received reconstruction using pericranial flaps as the defects were large and pedicled flaps using the mucosa of the nasal cavity were unavailable.

Table 4
Univariate Cox proportional hazard analysis of 25 SCC-NC&ES patients.

Variable	Score	No. of patients	HR	95% CI	*P*-value
Medial wall or floor of the orbit extension					
No	0	15	0.28	0.07–0.93	0.038
Yes	1	10			
Pterygoid plates extension					
No	0	23	0.03	<0.01–0.29	0.001
Yes	1	2			
Orbital apex extension					
No	0	21	0.1	0.03–0.41	0.003
Yes	1	4			

Abbreviations: HR, hazard ratio; CI, confidence interval.

CRT has received little attention with regard to the treatment of sininasal cancer [10]. In this study, CRT without NAC was applied in 2 patients, but failed. NAC followed by CRT was also performed for 2 patients, one of whom remains alive without disease to date. Hanna et al. reported that NAC is a promising technique that may improve treatment outcomes for patients with SCC of the paranasal sinuses [11], and NAC followed by CRT is also considered to be an option for locally advanced NC&ES.

We previously reported the efficacy of RADPLAT for the treatment of tumors in the nasal cavity and the paranasal sinus [3]. However, we did not focus on SCC of the NC&ES in that study. As we previously reported, RADPLAT is considered to be effective for the treatment of patients with locally advanced SCC of the nasal vestibule, with excellent cosmetic results reported [5]. As for NC&ES, tumors are expected to be mainly supplied by the external carotid system, but also partially supplied by the internal carotid system, such as the anterior and posterior ethmoid arteries, particularly when the tumors arise from ethmoid sinus. However, the external carotid system provided the main supply to the tumor

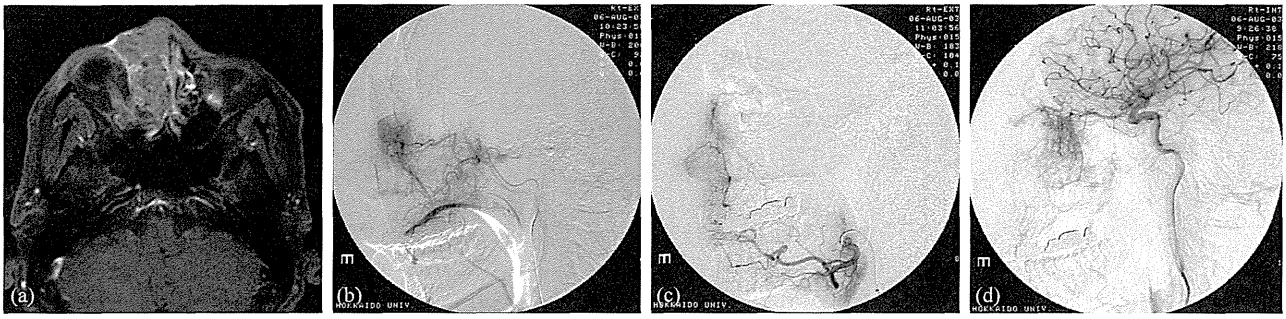

Fig. 3. MRI findings from a 57-year-old man with a right ethmoid sinus cancer that was classified as T4aN0M0 are shown (a). Lateral subtraction angiograms of the right internal maxillary artery (b), right facial artery (c), and right internal carotid artery (d) are shown. These indicated that the tumor was covered by not only the external carotid system (the internal maxillary and facial arteries) but also the internal carotid system. Cisplatin was infused from the external carotid system alone. However, the patient is currently alive without disease after 11 years of follow up.

in most cases. We have infused cisplatin into the external carotid system, but not into the internal carotid system to avoid CNS and optic complications (Fig. 3). As a result, cisplatin was infused from the internal maxillary artery in all 8 patients, the facial artery in 3 patients, and the transverse facial artery in 2 patients. In the remaining patient with T4a ethmoid cancer, angiography revealed that the tumor was not supplied by the external carotid system at all. Therefore, RADPLAT was not indicated in this case, and the patient received IV-CRT. Acute toxicity (≥grade III) was observed in only 2 of 8 patients (25%), both of whom experienced nausea/vomiting (grade III). With regard to late adverse reactions, brain necrosis (grade II) was observed in one patient. Three patients experienced ocular/visual problems (grade III to IV), but all of them required orbital exenteration if surgery were indicated. Although ocular/visual problems were observed in patients with tumors invading the orbit, the primary disease was successfully controlled by RADPLAT in 7 of 8 patients. Therefore, RADPLAT is a sound option for T4 NC&ES.

Generally, in sinonasal malignancies, the prognosis is worse for SCCs than for adenocarcinomas. Further, primary tumors of the maxillary sinus have a better prognosis than those of the ethmoid sinus [12,13]. Although there have been no reports focusing on SCCs of NC&ES, Dulguerov et al. reported that the 5-year actuarial specific survival rate of patients with SCC of the nasal and paranasal sinus treated between 1975 and 1994 was 60% [13]. Cantu et al. reported that in 33 cases of SCC of the ethmoid sinus treated between 1968 and 2003, the 5-yr overall survival was 18.7% [12]. In this study, despite 14 out of 25 patients having T4 disease, the 5-yr overall survival was 52.3%, although it might be inappropriate to compare our results with those of the previous studies.

Limited disease (T1–2) should be treated by surgery, if the surgical margin is close or positive and postoperative radiotherapy is indicated. Locally advanced and resectable disease (T3–T4a) should be treated by a combination of surgery followed by adjuvant radiotherapy or radiotherapy with chemotherapy. Unresectable tumors (T4b) or patients who refuse surgery should be treated by radiotherapy with chemotherapy. RADPLAT is another option for the treatment of these patients. Although RADPLAT is not mentioned in the NCCN guidelines, we consider it to be one of the chemoradiotherapy regimens. As to surgical approach, the most important thing is the achievement of negative margins with a good view regardless of whether an open or endonasal endoscopic approach is used. However, to improve the survival and quality of life after therapy, the indication of endoscopic endonasal surgery without an open approach and the means by which skull base defects are reconstructed need to be resolved. In addition, further is needed to develop non-surgical approaches for advanced disease, such as induction chemotherapy and RADPLAT.

Conflict of interest

All the authors hereby declare that they have no conflict of interest.

Acknowledgments

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