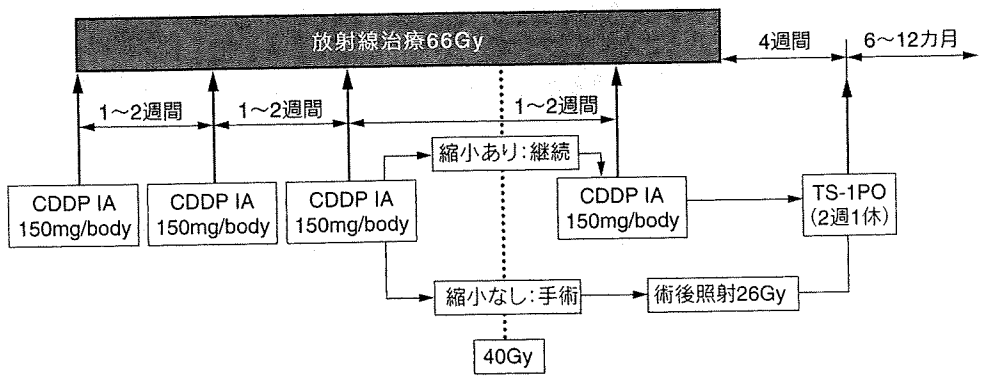

図 1　放射線併用超選択的動注化学療法のレジメン

能であり，術後の機能も満足のいく結果が得られる。深部への浸潤傾向が強い症例の場合は切除後の欠損が大きく，遊離組織移植や有茎皮弁による再建が必要となる。このような症例のうち手術治療に同意が得られなかった症例には，放射線併用動注療法を行っている。

以前行っていた動注の局所制御率が低かった原因として，口腔底癌は腫瘍容積が他の頭頸部癌と比べて大きい，下顎骨に囲まれているため放射線の効果が低下する，薬剤感受性の違い，などが考えられた。そこでこれらをクリアーするため，1回の動注で投与するCDDPの量を増やし，さらに動注の間隔を短縮し，総投与量の増加を図った。

現在では，放射線を66 Gy照射する間にCDDP 150 mg/body投与を1～2週間ごとに4回以上行っている。終了後はadjuvant chemotherapyとして6～12カ月間TS-1の内服投与を行っている（**図1**）。頸部リンパ節転移は，径の大きな症例を動注の対象としている。原発巣の制御が第一目的であるため，残存した頸部リンパ節転移は頸部郭清術で救済できればよいと考えている。

Ⅳ．症例の呈示

口腔底癌に対し動注療法を施行した症例を示す。

〔**症例**〕 58歳，男性。

主　訴：舌右側の痛み。

現病歴：舌右側の痛みのため他院耳鼻咽喉科を受診し，右口腔底後方に腫瘍を指摘された。当科を紹介受診し，生検で扁平上皮癌と診断された。CTで口腔底深部に浸潤する腫瘍と右上頸部にリンパ節転移を認めた（**図2-a**）。

診　断：口腔底癌，T3N1M0，stage Ⅲ。

治療経過：手術では遊離組織移植による再建術が必要と考えられた。患者と相談のうえ放射線化学療法を施行することにした。放射線照射（66 Gy/33回）を開始し，同時にCDDPを用いた動注化学療法を施行した（**図2-b，c**）。1回投与量は，原発巣には150 mg，頸部リンパ節には50 mgとした。照射中に動注を4回施行し，原発巣，頸部リンパ節転移ともに消失した。退院後はTS-1 100 mg/日を2週服薬1週休薬で継続している。治療終了後6カ月経過し，現在まで再発を認めていない。

Ⅴ．口腔底癌に放射線化学療法を行う際に留意する点

1．放射線化学療法の適応について

金沢大学を含め，口腔底癌に対する放射線化学療法で，手術を上回る治療成績のものは現在まで報告されていない。したがって現段階では，術後機能障害が軽度であると予想される口腔底癌late T2・T3症例に対する治療の第一選択は手術と考える。患者主導で治療法を決定すべきとはいわれているが，各施設での両者の治療成績，術後機能障害の可能性，抗癌剤の副作用，放射線障害（特

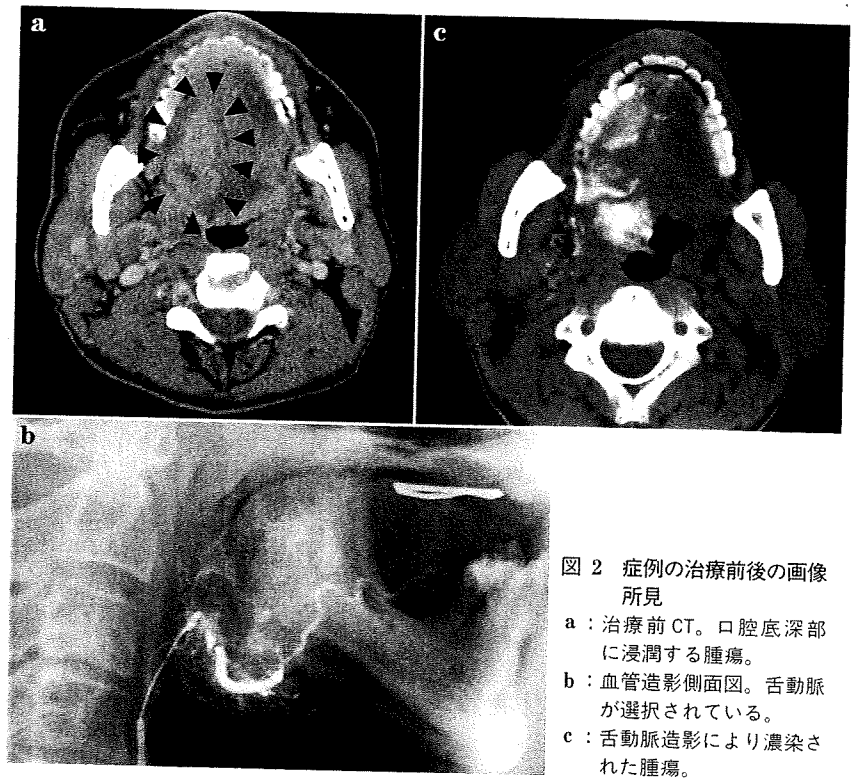

図 2　症例の治療前後の画像所見
a：治療前 CT。口腔底深部に浸潤する腫瘍。
b：血管造影側面図。舌動脈が選択されている。
c：舌動脈造影により濃染された腫瘍。

に下顎骨骨髄炎や唾液分泌障害，誘発癌）などを説明したうえで，まずは手術を勧め，手術拒否例には放射線化学療法を勧める，というのが一般的な対応と考える。

現段階では放射線化学療法の適応は，手術拒否例や拡大手術の施行が困難な症例に限られる。しかし臓器温存を目指した治療が求められている現在，放射線化学療法の治療成績の向上に伴い，手術以外の治療法を求められる機会は今後増加するであろう。さらに late T 2・T 3 症例であっても術後機能低下が予想されるような症例にとっては，手術治療に変わる放射線化学療法の確立は重要である。

2．抗癌剤の投与量，放射線の効果について

喉頭・下咽頭癌に対する動注では 1 回投与量 CDDP 100 mg，総投与量 200～300 mg で満足のいく局所制御率が得られるが，口腔癌は腫瘍容積が大きいため，この投与量では不十分である。過去の経験から 1 回投与量は少なくとも CDDP 150 mg，総投与量も 600 mg 以上は必要であろう。放射線照射に関しては，口腔底は下顎骨と歯牙の裏面となるため照射野の設定が難しかった。しかし IMRT の出現で，より正確な照射野の設定が可能となった。今後 IMRT による局所制御率が向上する可能性がある。

3．再発時の手術について

放射線化学療法後は組織の癒着が強く，頸部筋膜解剖もわかりにくくなる。そのため一般的に再発時の救済手術は難易度が高く，手術手技に熟練を要する。また創傷治癒遅延や感染など術後合併症の増加，再建手術が必要となる症例では皮弁壊死や瘻孔形成が問題となる。口腔底癌に対し放射線化学療法を施行する際には，再発時の救済手術を安全に行える体制が整っていることも重要である。

まとめ

口腔底は非常に狭い領域であるため，口腔底癌

late T 2・T 3 症例に対する局所切除は口腔底の欠損範囲が大きく，何らかの再建を必要とする症例が多い。その結果，咀嚼・構音・嚥下機能に大きな機能障害が生じることになる。これらの症例に対して放射線化学療法により臓器が温存されたまま治療が可能であればQOLに対する貢献は大きい。しかし，口腔底癌の症例数は少なく，有効な放射線化学療法の確立のためには多施設合同での臨床研究も必要である。

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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

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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.

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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,

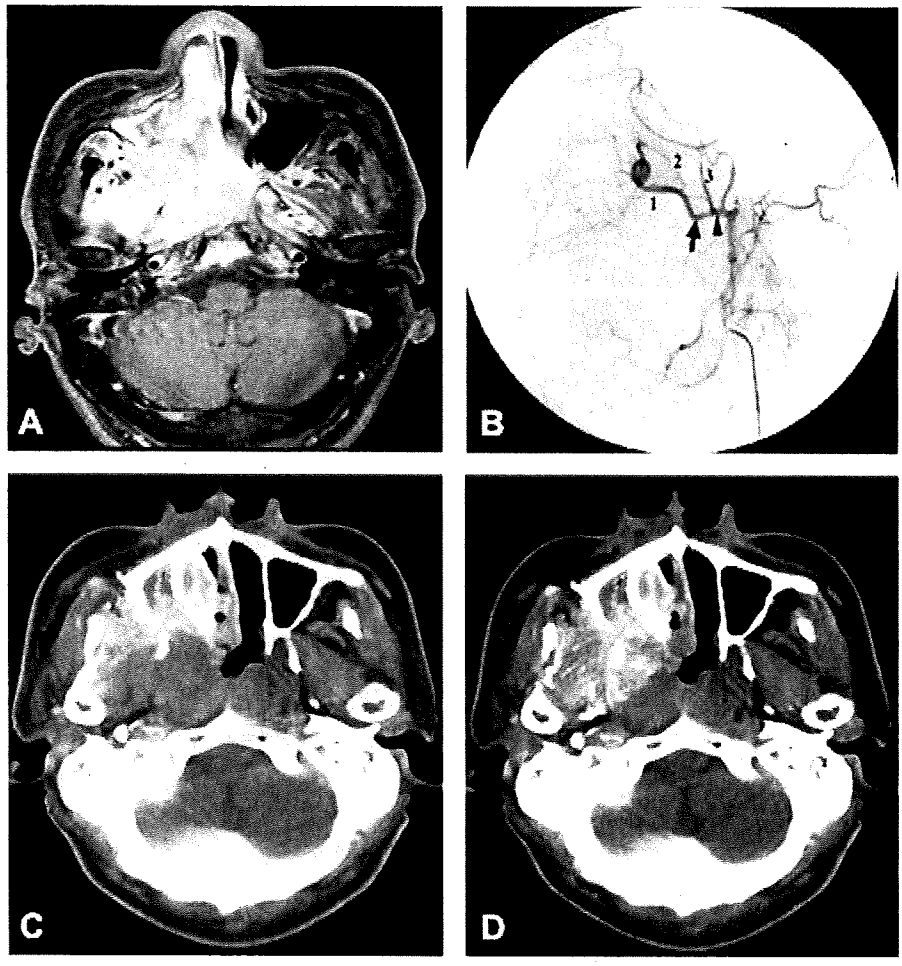

FIGURE 1. (A) Findings from a 57-year-old man with a right maxillary sinus cancer that was classified as T4bN2bM0 are shown. (B) A lateral subtraction angiogram of right external carotid artery is shown. The internal maxillary artery (indicated by 1), accessory meningeal artery (indicated by 2), and 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

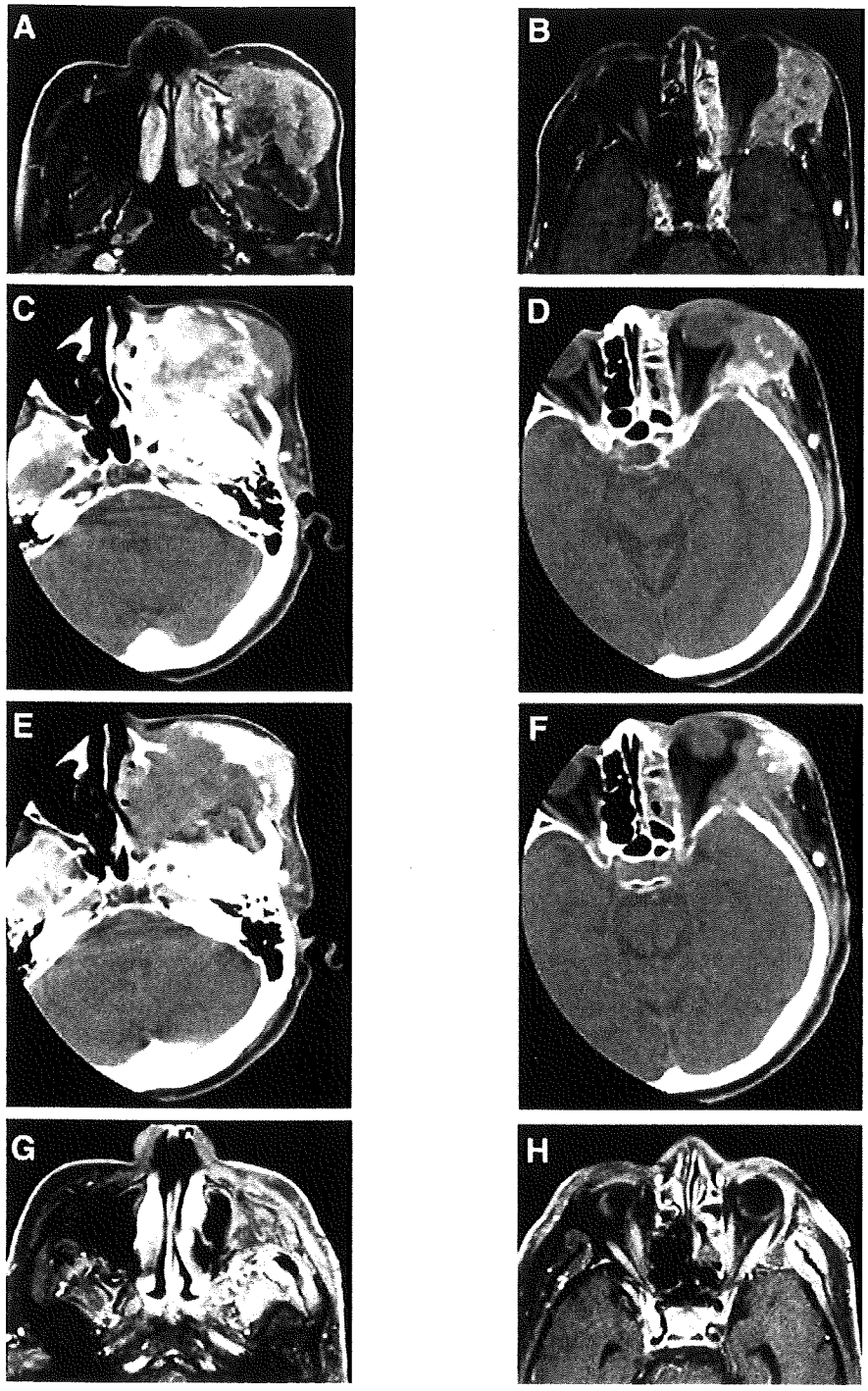

FIGURE 2. (A and B) Findings from a 70-year-old man with a left maxillary sinus cancer classified as T4bN0M0 are shown. (C and D) Tumor enhancement was identified with intra-arterial computed tomographic arteriography (IA-CTA) of the internal maxillary artery. The facial tissue that was anterior and 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

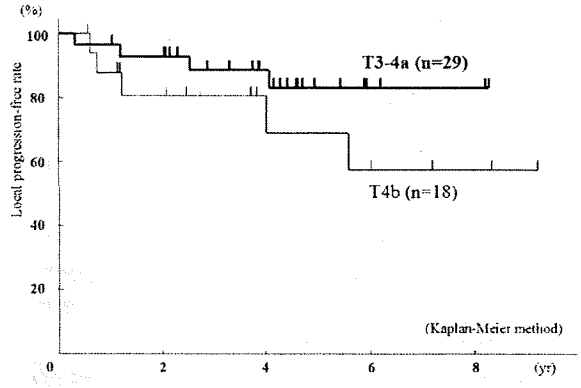

FIGURE 3. Local progression-free survival rate according to T classification is shown in 47 patients with cancer of the nasal cavity and paranasal sinuses.

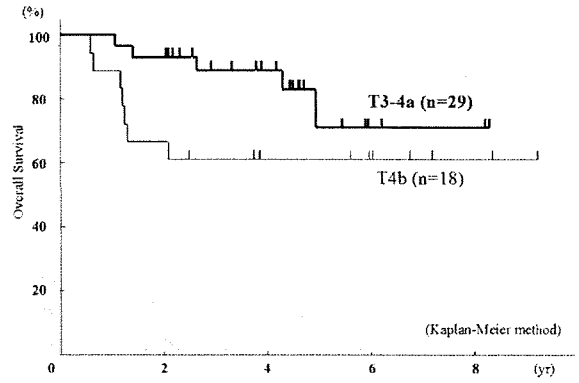

FIGURE 4. Overall survival according to T classification is shown in 47 patients with cancer of the nasal cavity and paranasal sinuses.

(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.

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ORIGINAL ARTICLE

Complications of Skull Base Surgery: An Analysis of 30 Cases

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ABSTRACT

Objectives: To evaluate the risk factors for perioperative complications among patients undergoing craniofacial resection for the treatment of skull base tumors. Design: Retrospective analysis. Participants: The study group comprised 29 patients with skull base tumors (22 malignant and 7 benign) who underwent 30 craniofacial resections at Hokkaido University Hospital between 1989 and 2006. Of these cases, 21 had undergone prior treatment by radiation (16 cases), surgery (7 cases), or chemotherapy (1 case). Moreover, 19 needed extended resection involving the dura (11 cases), brain (5 cases), orbit (12 cases), hard palate (5 cases), skin (3 cases), or cavernous sinus (2 cases). Main outcome measures: Perioperative complications and risk factor associated with their incidence. Results: Perioperative complications occurred in 12 patients (40%; 13 cases). There was a significant difference between complication rates for cases with and without prior therapy (52.4% vs. 11.1%). The complication rate for dural resection cases was 81.8%. There was a significant difference between complication rates for cases with and without dura resection. No postoperative mortality was reported. Conclusions: Craniofacial resection is a safe and effective treatment for skull base tumors. However, additional care is required in patients with extended resection (especially dural) and those who have undergone prior therapy.

KEYWORDS: Complications, craniofacial resection, skull base surgery

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Ketcham and colleagues[1] first reported on the combined transcranial and transfacial approach for tumors of the paranasal sinuses involving the anterior skull base in 1963. Since then, improved radiological imaging techniques have allowed surgeons to evaluate the tumor extent more easily. Moreover, the use of microvascular free-flap transfer has allowed indications of craniofacial resection to be extended to patients with three-dimensional defects and wide exposure of the contents of the endocranium. However, extended resection surgery often has severe complications.

In the current study, we reviewed 30 cases of skull base surgery for tumors involving the anterior and middle cranial base. We calculated the survival and complication rates, and analyzed the risk factors associated with the incidence of perioperative complications.

PATIENTS AND METHODS

Patients

Between 1989 and 2006, a total of 30 skull base surgeries were performed in 29 patients with tumors involving the anterior and/or middle cranial fossa at the Hokkaido University Hospital, Sapporo, Japan (Table 1). This group comprised 22 males and 7 females, with a median age of 60 years (range, 26 to 71 yrs). In total, 22 of the patients had malignant tumors (squamous cell carcinoma in 11 cases, olfactory neuroblastoma in 5 cases, adenoid cystic carcinoma in 3 cases, adenosquamous cell carcinoma in 2 cases, and rhabdomyosarcoma in 1 case). The remaining seven patients had benign tumors (hemangioma in one case, trigeminal nerve neurinoma in one case, frontal sinus cyst in one case, giant cell tumor in one case, fibrous dysplasia in one case, inverted papilloma in one case, and pigmented villonodular synovitis in one case). The patient with hemangioma underwent skull base surgery twice. In total, 21 of the cases had undergone prior therapy.

Table 1 Patient Demographics

Characteristic	*n*
Total	29
Age group (yrs)	
20–39	4 (13.8%)
40–49	5 (17.2%)
50–59	4 (13.8%)
60–69	15 (51.7%)
70+	1 (3.4%)
Gender	
Male	22 (75.9%)
Female	7 (24.1%)
Medical comorbidity	
Present	5 (17.2%)
Absent	24 (82.8%)
Pathology	
Adenoid cystic carcinoma	3 (10.3%)
Olfactory neuroblastoma	5 (17.2%)
Squamous cell carcinoma	11 (37.9%)
Adenosquamous cell carcinoma	2 (6.9%)
Rhabdomyosarcoma	1 (3.4%)
Benign	7 (24.1%)
Prior therapy*	
Present	21 (70%)
Surgery alone	4 (13.3%)
Radiation alone	13 (43.3%)
Surgery + radiation	3 (10%)
Chemotherapy alone	1 (3.3%)
Absent	9 (30%)

*Based on 30 cases of skull base surgery.

Among the patients with malignant tumors, 16 cases had undergone prior radiotherapy (30 to 65 Gy), 5 cases had undergone previous surgery, and 1 case with olfactory neuroblastoma had undergone prior chemotherapy (cisplatin). Among the patients with benign tumors, two cases had undergone previous surgery, one case had recurrence of inverted papilloma, and one case had recurrence of hemangioma in the middle cranial fossa with facial nerve paralysis.

Methods

In total, 25 cases (83.3%) were treated by the anterior fossa approach with a lateral rhinotomy skin incision and/or a coronal arch-shaped skin

Table 2 Details of Skull Base Surgery*

Feature	*n*
Type of approach	
Anterior fossa	25 (83.3%)
Middle fossa	5 (16.7%)
Extent of resection	
Orbit	12 (40%)
Hard palate	5 (16.7%)
Dura	13 (43.3%)
Brain	5 (16.7%)
Skin	3 (10%)
Cavernous sinus	2 (6.7%)
Reconstruction	
RAMC free flap	9 (30%)
FA free flap	3 (10%)
Locoregional flap alone	18 (60%)

*Based on 30 cases of skull base surgery.
RAMC, rectus abdominis myocutaneous; FA, forearm.

incision (Table 2). A total of five cases of benign tumor received middle cranial resection with a temporal skin incision. All of the cases underwent skull base reconstruction. We used 3 forearm (FA) free flaps with microvascular anastomosis, 9 rectus abdominis myocutaneous (RAMC) free flaps with microvascular anastomosis, and 18 locoregional flaps.

In total, 19 of these cases needed extended resection involving the dura (11 cases), brain (5 cases), orbital content (12 cases), hard palate (5 cases), skin (3 cases), or cavernous sinus (2 cases). All of the cases that required extended resection had malignant tumors.

The clinical histories of the patients were ascertained from their medical records retrospectively. The follow-up period ranged from 9 to 210 months (median, 44 mos). We estimated the medical comorbidity using the Adult Comorbidity Evaluation (ACE)-27 index system; this was derived from the original Kaplan-Feinstein Index (KFI), which was developed to assess comorbidity in diabetes mellitus,[2] and has subsequently been modified and validated by Piccirillo[3] to include terms relevant to cancer. We classified five patients (17.2%) who were judged to be grade 2 or 3 according to the ACE-27 index as having medical comorbidities; four of these patients had cardiovascular system complications (hypertension in two, ischemic heart disease in one, and arteriosclerosis obliterans in one), and the remaining patient had respiratory system complications (pulmonary emphysema).

The survival rates were calculated, after the initial visit to our hospital, using the Kaplan-Meier method, and were compared using the log-rank test. A p value < 0.05 was considered statistically significant. Risk factors for perioperative complications were compared using Fisher's test.

RESULTS

The average operation time was 10.4 hours (range, 4.5 to 18 hrs). The figure for patients who underwent free-flap reconstruction was 13.9 hours, whereas that for patients who underwent other types of reconstruction was 7.8 hours. The average operation time for resection with free-flap reconstruction was significantly longer ($p < 0.01$). Otherwise, the figure for malignant cases was 12.1 hours and that for benign cases was 6.1 hours. The average operation time for malignant cases was significantly longer than that for benign cases ($p < 0.01$).

The average blood loss during operation was 1208 mL (range, 20 to 8360 mL). The figure for malignant cases was 1482 mL whereas that for benign cases was 388 mL. The malignant cases experienced significantly higher blood loss than the benign cases ($p < 0.01$).

Among all of the cases, the overall 5-year survival rate was 63.7%. In the 22 patients with malignant tumors, the figure was 51.3%. Table 3 shows comparative data on the overall 5-year survival rate among patients with malignant tumors. There were no significant differences in survival rate associated with age or with brain or dural resection. However, there was a significant difference in survival rate between cases with and without medical comorbidity ($p < 0.005$).

In total, 13 perioperative complications were reported in 12 of the cases (40%); these comprised

Table 3 Overall Survival Rate among Patients with Malignant Tumors

Variable	5-Year Survival Rate	*p* Value
Total ($n = 22$)	51.3%	
Age		
< 60 years ($n = 9$)	77.8%	
≥ 60 years ($n = 13$)	31.0%	0.09
Medical comorbidity		
Present ($n = 5$)	0.0%	
Absent ($n = 7$)	67.0%	0.0002
Brain resection		
Present ($n = 5$)	20.0%	
Absent ($n = 17$)	62.0%	0.15
Dural resection		
Present ($n = 13$)	51.3%	
Absent ($n = 9$)	50.0%	0.97

6 wound complications, 4 central nervous system complications, 1 systemic complication, and 2 other types of complication (Table 4). The wound complications were four local infections, one hematoma, and one bleed. The central nervous system complications were four cases of meningitis. The systemic complication was one case of deep vein thrombosis. The other types of complication were two donor-site complications of the RAMC flap (herniation and abscess).

Table 4 Perioperative Complications*

Type of Complication	*n*
Complications	
Present	12 (40%)
Absent	18 (60%)
Wound complications	
Local infection	4 (13.3%)
Hematoma	1 (3.3%)
Bleeding (intraoperative)	1 (3.3%)
Central nervous system complication	
Meningitis	4 (13.3%)
Systemic complication	
Deep vein thrombosis	1 (3.3%)
Others	
RAMC donor site herniation	1 (3.3%)
RAMC donor site abscess	1 (3.3%)
Perioperative mortality	0 (0%)

*Based on 30 cases of skull base surgery.
RAMC, rectus abdominis myocutaneous.

Table 5 Factors Associated with the Incidence of Perioperative Complications*

Variable	Complication Rate	*p* Value
Age		
< 60 years	6/14 (42.9%)	
≥ 60 years	6/16 (37.5%)	0.94
Medical comorbidity		
Present	2/5 (40%)	
Absent	10/25 (40%)	
Pathology		
Malignant	11/22 (50%)	
Benign	1/8 (12.5%)	0.09
Prior therapy		
Present	11/21 (52.4%)	0.049
Absent	1/9 (11.1%)	
Dural resection		
Present	9/11 (81.8%)	0.0012
Absent	3/19 (15.8%)	
Brain resection		
Present	3/5 (60%)	0.36
Absent	9/25 (36%)	
Orbital resection		
Present	6/12 (50%)	0.59
Absent	6/18 (33.3%)	
Hard palate resection		
Present	2/5 (40%)	
Absent	10/25 (40%)	
Free flap reconstruction		
Present	4/12 (33.3%)	0.82
Absent	8/18 (44.4%)	

*Based on 30 cases of skull base surgery.

Among the malignant tumor patients, 11 of the 22 cases (50%) had complications (Table 5). Among the benign tumor patients, only one of the eight cases (12.5%) had a complication (bacterial meningitis). There was no significant difference between the complication rates of patients with malignant and benign tumors.

In the group without prior therapy, one of the eight cases (11%) had complications. In the group with prior therapy (including surgery, radiation, and chemotherapy), 11 of the 21 cases (52.4%) had complications. There was a significant difference between the complication rates of the groups with and without prior therapy ($p < 0.05$).

Table 5 shows the factors that were associated with the incidence of perioperative complications.

In total, 9 of the 11 (81.8%) dural resection cases had some complications: of them, 5 (45.5%) had local problems (infection, development of abscess, and bleeding), 2 (18.2%) had meningitis, 1 (9.1%) had deep vein thrombosis, and 1 (9.1%) had RAMC donor-site herniation. There was a significant difference between the complication rates of the groups with and without dural resection. However, there was no significant difference between the complication rates of the groups with and without the other types of extended resection. Moreover, there was no significant difference between the complication rates of the groups with and without medical comorbidities.

DISCUSSION

Since Ketcham and colleagues[1] reported the combined transcranial and transfacial approach for the resection of paranasal sinus tumor involving the anterior cranial fossa more than 40 years ago, skull base surgery has been put into practice throughout the world and has improved in safety. However, skull base surgery still requires a relatively long operation time, and the damage to patients can sometimes be severe. Particular attention must be paid to the complications, some of which can cause postoperative death. Here we analyzed the outcomes and perioperative complications of skull base surgery cases in our hospital, and described their characteristics.

Recent reports have shown the complication rate of skull base surgery to be 33 to 54.7%.[4–10] In our current series, the complication rate was 40%, which was comparable with these reports.

It has been unclear from previous studies whether prior therapy and the extent of resection are associated with the incidence of perioperative complications. In a collaborative study, Ganly and associates[9] reported that dural and/or brain invasion cases had significantly higher complication rates than cases without invasion; they also reported a significant difference in complication rates between cases with and without prior radiation (44% versus 34%; $p = 0.001$). However, Deschler and colleagues[11] reported no significant difference between the complication rates for patients with previous craniotomy, radiation therapy, or chemotherapy compared with those without prior therapy ($p > 0.5$). In addition, Kraus et al[5] reported no significant difference between the complication rates for patients with and without previous therapy ($p = 0.21$), or between patients with invasion (of the palate, orbit, dura, and brain) and those without invasion. In our current series, we found that prior therapy and dural resection were risk factors for perioperative complications. These discrepancies could be caused by differences in patient characteristics and surgical techniques between institutions. We predicted that prior therapy could be a risk factor for the incidence of perioperative complications. Moreover, in dural resection cases, there were many instances of local complications (45.5%) and meningitis (18.2%). It is therefore important to employ preoperative and/or postoperative antibiotict therapy for patients with dural invasive tumors.

Recent studies have reported postoperative death rates of 2 to 7.6%.[4–9,11] In our current series, there was no postoperative death. We therefore concluded that our indications for skull base surgery were appropriate.

For patients with malignant tumors, the overall 5-year survival rate for cases with skull base surgery has been reported as 52 to 56%.[4–6,12] In our current series, the overall 5-year survival rate for patients with malignant tumors ($n = 22$) was 51.3%. Shah and colleagues[7] reported that the survival rate was significantly better for patients whose tumors could be excised with limited resection compared with those requiring an extended procedure. Our current data showed that the 5-year survival rates for patients with and without brain resection were 20% and 62%, respectively. However, we were unable to find a statistically significant difference between patients who underwent limited and extended resection. Furthermore, none of the patients with medical comorbidities survived for more than 5 years. All of these cases

had disease-specific death. We therefore concluded that medical comorbidity was an important risk factor for survival.

We performed skull base surgery in eight cases with benign tumors. Our general policy was to observe cases of benign tumor without symptoms; however, we judged that patients with some functional loss, such as facial nerve paralysis, needed a reduction of the tumor to allow the recovery of nervous function. We also judged that patients with a premalignant tumor (such as an inverted papilloma) invading the skull base needed craniofacial surgery for total resection. In total, five of the eight cases were treated using the middle fossa approach with a temporal skin incision. These cases had no complications. Only one case of inverted papilloma with anterior craniofacial resection had bacterial meningitis. We therefore concluded that our approach for skull base surgery of benign tumors was safe, although additional attention must be given to complications such as meningitis.

CONCLUSIONS

Craniofacial resection has been developed into a safe and effective procedure for the treatment of tumors involving the skull base. Our analysis showed that dural resection and prior therapy were risk factors for the incidence of perioperative complications. Additional care must therefore be taken with patients who have undergone prior therapy. Furthermore, local complications (45.5%) and meningitis (18.2%) were recognized in dural resection cases. A preoperative and/or postoperative strategy against local infection and meningitis is therefore necessary.

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ORIGINAL ARTICLE

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Antiemetic effects of granisetron and dexamethasone combination therapy during cisplatin-containing chemotherapy for head and neck cancer: dexamethasone dosage verification trial

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Abstract

Background. Chemotherapy-induced nausea and vomiting (CINV) remains a significant problem for patients and is associated with a substantial deterioration in quality of life; appropriate use of antiemetic drugs is crucial in maintaining the quality of life in patients undergoing chemotherapy.

Methods. This randomized, crossover trial evaluated the antiemetic efficacy and safety of 8 mg per day (low-dose) and 16 mg per day (standard-dose) dexamethasone, in combination with the 5-HT_3 receptor antagonist granisetron, in 36 patients receiving cisplatin (CDDP)-containing chemotherapy for head and neck cancer. Following chemotherapy, the antinausea/vomiting inhibition rate for each dexamethasone dose was measured.

Results. During the 24-h period following administration of chemotherapy (acute phase), the antinausea/vomiting inhibition rates (no nausea and no episodes of vomiting) for 8 mg and 16 mg dexamethasone were comparably high (58.3% and 63.8%, respectively; $P = 0.8092$). Similar results were seen on days 2–5 following chemotherapy. Efficacy during the acute phase, based on the number of instances of vomiting and degree of nausea, was also comparably high for the two dexamethasone doses (overall efficacy rates were 94.4% and 88.8%, respectively, for 8 mg and 16 mg dexamethasone; $P = 0.7637$). Both doses maintained an 80% or higher response rate until day 3, and neither dose produced severe side effects.

Conclusion. The results suggest that granisetron and dexamethasone combination therapy is useful in controlling acute and delayed nausea and vomiting induced by CDDP-containing chemotherapy for head and neck cancer. Furthermore, 8 mg and 16 mg dexamethasone have equivalent antiemetic efficacy.

Key words Chemotherapy · Nausea · Vomiting · Granisetron · Dexamethasone

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Introduction

The optimal strategy to avoid chemotherapy-induced nausea and vomiting (CINV) continues to present challenges for the oncologist and pharmacotherapist, and appropriate use of antiemetic drugs is crucial in maintaining the quality of life in patients undergoing chemotherapy. Cisplatin (CDDP)-containing chemotherapy is becoming a widespread treatment choice for head and neck cancer. However, as nausea and vomiting frequently occur following CDDP administration, controlling these symptoms is a crucial component of the overall treatment plan.

The recent advent of 5-HT_3 receptor antagonists has made it possible to control the acute nausea and vomiting that often follow immediately after CDDP-containing chemotherapy. While these agents are effective in the acute phase, they are not sufficiently effective in controlling delayed nausea and vomiting occurring beyond the 24-h period following chemotherapy administration. To address this issue, the antiemetic efficacy of 5-HT_3 receptor antagonists in combination with drugs that exhibit a delayed antiemetic effect has been investigated, with results suggesting that steroids, such as dexamethasone, offer a promising adjunct to 5-HT_3 receptor antagonists.[1,2]

Various national and international treatment guidelines state that when using dexamethasone in combination with 5-HT_3 receptor antagonists to control chemotherapy-induced nausea, the recommended dose of dexamethasone is 20 mg for preventing acute nausea and vomiting and 16 mg for preventing delayed nausea and vomiting.[3] However, the appropriateness of these doses for the Japanese population is questionable, for several reasons. Firstly, in Japan, the dosage of CDDP used in the treatment of head