Retrospective Evaluation of Surgical Intervention following Chemo- and Radiotherapy of Maxillary Sinus Cancers

Keigo KUDO, Yumi SATOH, Mitsuhiro ENDO,
Kiyoshi SEGAWA, Yoshiyasu FUKUTA, Mitsumasa YOKOTA
and Yukio FUJIOKA

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Abstract

During the past 15 years, 30 patients with squamous cell carcinomas of the maxillary sinus were treated by modified partial maxillectomy following chemo- and radiotherapy, taking care to preserve facial contour and function as far as possible. Follow-up evaluation showed that local recurrences, and regional lymph node and distant metastases were more frequent in T4 patients than in T3 patients. Evaluation of the histopathological effects of preoperative chemo- and radiotherapy at the time of surgery showed that T4 patients tended to have a poorer response to the treatment than T3 patients. Analysis according to the direction of primary tumor extension showed that the incidence of local recurrence was higher in the superolateral type, whereas that of regional lymph node metastasis was higher in the medial type. The cumulative 5-year survival was high (72.2%) in Stage III patients and low (22.5%) in Stage IV patients. The overall rate was 55.4%. The treatment produced relatively good outcomes in T3 patients but poor outcomes in T4 patients. These findings indicate that T4 carcinoma of the maxillary sinus must be managed initially by a combination of irradiation and multi-chemotherapeutic drugs, and then treated by more extensive surgical resection.

Introduction

The 5-year survival following treatment of maxillary sinus cancers has generally been estimated to be less than 50%^[1-4]. On the other hand, it has been reported that esthetic and functional preservation of the maxillofacial structure and also improvement of the therapeutic results can be achieved by simultaneous treatment consisting of intraarterial administration of antitumor agents and irradiation followed by continuous daily necrotomy of the tumor and antrotomy^[5,6]. Recently,

工藤啓吾 佐藤友美 遠藤光宏 瀬川 清 福田喜安 横田光正 藤岡幸雄

*First Department of Oral and Maxillofacial Surgery, School of Dentistry, Iwate Medical University.
To whom all correspondence should be addressed: Dr. Keigo KUDO, First Department of Oral and Maxillofacial Surgery, School of Dentistry, Iwate Medical University, 1-3-27 Chuo-Dori, Morioka, Iwate 020, JAPAN.*

it has been reported that a 5-year survival of more than 50% was obtained by surgical excision following a combination of chemo- and radiotherapy^[7,8].

In 30 patients with squamous cell carcinomas of the maxillary sinus, we have attempted to preserve the normal surrounding tissues as extensively as possible by partial resection of the maxilla following combined administration of intraarterial or intravenous antitumor agents and irradiation. This mode of treatment produced a good outcome in T3 patients. In contrast, not only local recurrences but also cervical and distant metastases were frequent in T4 patients, whose prognoses were mostly poor. The aim of our present study was to investigate the relationship of therapeutic outcome, local recurrence, regional lymph node metastasis and distant metastasis to the size of the primary tumor, the histopathological effects after a preoperative combination of chemo- and radiotherapy and the direction of primary tumor extension.

Materials

During a 15-year period from 1974 to 1988, 30 patients with squamous cell carcinomas of the maxillary sinus were treated at our clinic. The patients comprised 21 men and 9 women ranging in age from 30 to 83 years (mean 56.9 yr). More than 3 years have passed since the treatment in all cases. On examining the differentiation of tumor tissue in the biopsy specimens, 12 of them were Grade I, 14 were Grade II and 4 Grade III. By the 1987 UICC TNM classification^[9], only 2 patients were categorized as T2N0M0. Fourteen were categorized as T3N0M0, 4 as T3N1M0, 1 as T3N2bM0, 6 as T4N0M0, 1 as T4N1M0 and 2 as T4N2cM0. By stage classification, 2 patients were Stage II, 18 were Stage III and 10 were Stage IV. Thus, advanced cases accounted for the majority of the patients (Table 1).

On the basis of X-ray, CT, MRI and macroscopic findings during surgery, the 30 primary tumors were divided into the following 6 types according to the direction of tumor extension, after SAKAI et al.^[10]; 14 inferolateral type, 6 superolateral type, 2 anterior type, 2 posterior type, 5 inferomedial type and 1 superomedial type.

Table 1 TNM classification and staging by the 1987 UICC classification^[9]

Stage	N	T1	T2	T3	T4	Total
II	N0	0	2	14	6	22
III	N1	0	0	4	1	5
IV	N2	0	0	1	2	3
	N3	0	0	0	0	
Total		0	2	19	9	30

Methods

The mode of our chemo- and radiotherapy was modified during the study period as follows: in 2 patients treated during 1975-1976, the therapy consisted of irradiation up to a total dosage of 40 or 60 Gy and intraarterial 5-fluorouracil (5-FU) at a dose of 250 mg up to a total of 4,000-6,000 mg. In 18 patients treated

during 1976-1982, irradiation was reduced to a total dose of 10-16 Gy, and intraarterial 5-FU was also decreased to a dose of 125 mg up to a total of 625-1,000 mg. Peplomycin (PEP) was administered intraarterially or intravenously at a decreased dose of 5 mg up to a total of 25-40 mg. However, because 7 of 10 patients seen after 1983 had T4, irradiation for these patients was increased to a total of 30-40 Gy. Intraarterial 5-FU was administered at a dose of 125 mg up to an increased total of 3,750-5,000 mg. Intraarterial or intravenous PEP was administered at a dose of 5 mg up to an increased total of 30-60 mg. In some of the patients, however, the therapy was discontinued due to the development of side effects. Three patients seen in 1988 were managed by a combination therapy consisting of cis-diamminedichloroplatinum (CDDP) intraarterially at a dose of 50 or 90 mg up to a total of 100 or 180 mg, and PEP intraarterially at a dose of 5 mg up to a total of 25 mg or 5-FU intraarterially at a dose of 500 mg up to a total of 2,500 mg. This was combined with irradiation up to a total dose of 30-40 Gy. The antitumor agents were administered through the superficial temporal artery in 23 patients and intravenously in 7. For irradiation, ^{60}Co was used in 23 patients and Linac X-ray in 7, at a dose of 2 Gy.

The maxillary sinus was fenestrated intraorally in as many patients as possible, and tissue that had been necrotized by preoperative chemo- and radiotherapy was aspirated every day. Modified partial maxillectomy designed to preserve as much of the surrounding healthy tissue as possible, including the facial skin, eyes and palate, was performed 1-3 weeks after the preoperative chemo- and radiotherapy. Regions where residual tumor was suspected during surgery were additionally resected with care. The wounds were covered by 5-FU-impregnated gauze. Total neck dissection was performed on patients who had developed regional lymph node metastasis.

After discharge from the hospital, the patients were followed once fortnightly for the first 6 months, once monthly for the subsequent 1 year, once every 3 months for the subsequent 3 years and once every 6 months for the subsequent 5 years. For 1-2 years postoperatively, Tegafur or UFT was administered orally. Recurrent tumors were excised after administration of irradiation and/or antitumor agents.

Results

When local recurrences were examined in relation to primary tumor size, recurrence developed in 7 (77.8%) of the 9 T4 patients. Thus, the frequency of local recurrence was higher than that (19.1%, 4 cases) in the 21 T2 and T3 patients. When examined in relation to the direction of primary tumor extension, local recurrence appeared in all 6 cases of the superolateral type. This type had a greater tendency to develop local recurrence than the other types of primary tumor extension (Table 2). In 5 of the 11 patients who developed local recurrences, metastases to regional lymph nodes or lungs were found. In these 11, the local recurrences appeared at 2-12 months (mean 5.5 months) after surgery, except in 1 patient who developed local recurrence after 5 years and 6 months. After excision of the recurrent tumor, the eyeballs were enucleated in 3 patients. A facial skin defect resulted in 5 patients, for which secondary reconstruction was carried out in 3 using a

deltopectoral flap, and a facial epithesis was applied in 2. In the 2 T4 patients, on the other hand, the cranial dura mater was invaded by the primary tumor, and after resection these defects were immediately repaired using lyophilized dura. One patient survived without disturbance even after 10 years, but the other died of contralateral cerebral infarction.

Table 2 Number of local recurrences according to T-classification and direction of primary tumor extension

Primary tumor	Direction of primary tumor extension						Total
	Infero-lateral	Supero-lateral	Infero-medial	Supero-medial	Anterior	Posterior	
T2	1/ 1	—	—	—	—	0/1	1/ 2
T3	1/11	1/1	1/5	—	0/2	—	3/19
T4	2/ 2	5/5	—	0/1	—	0/1	7/ 9
Total	4/14	6/6	1/5	0/1	0/2	0/2	11/30

Cervical lymph node metastases before initial treatment were more frequent in the 18 patients with moderately or poorly differentiated types (33.3%, 6 cases) compared with the 12 patients with the well differentiated type (16.7%, 2 cases).

The histopathological effects of the preoperative chemo- and radiotherapy for the primary tumors were evaluated by grading on the basis of the concept of SHIMOSATO^[11] using specimens of the resected tumor tissues cut into slices at intervals of 1 cm. The effects were categorized on the basis of the lowest grade in the specimens (Table 3). As a result of the preoperative chemo- and radiotherapy, the tumors were categorized as Grade II b in both of the T2 patients. Of the 19 T3 patients, the tumors were categorized as Grade I in 5, Grade II a in 3, Grade II b in 7, Grade III in 2 and Grade IV in 2. In contrast, the tumors in the 9 T4 patients were categorized as Grade I in 4, Grade II a in 3 and Grade II b in 2. This indicates that the larger the primary tumors were, the less effective the preoperative therapy tended to be (Table 4). In the 11 Grade II b and III cases and the 4 Grade

Table 3 Criteria for evaluation of histopathological effect^[11] obtained by preoperative combination of radio- and chemotherapy

Grade I	Characteristic changes are noted in tumor cells but tumor structures have not been destroyed (there is no defect in tumor nests resulting from lysis of individual tumor cells).
Grade II	In addition to characteristic cellular changes, tumor structures have been destroyed as a result of disappearance of tumor cells. However, a variable number of viable cells still remain.
a	Destruction of tumor structures is mild in degree, i. e., viable tumor cells are frequently observed.
b	Destruction of tumor structures is severe in degree, i. e., viable tumor cells are scarce.
Grade III	Markedly altered, presumably nonviable tumor cells are present singly or in small clusters, and viable cells are hardly seen.
Grade IV	No tumor cells remain in any sections (local cure).
a	Extensive areas of coagulation necrosis are present.
b	Granulation tissue with or without small foci of necrosis including keratotic debris remains.
c	Only cicatrix is observed.

Table 4 Histopathological effect^[11] of preoperative combination chemo- and radiotherapy for squamous cell carcinoma of the maxillary sinus

Primary tumor	Histopathological effect by grade					Total
	I	IIa	IIb	III	IV	
T2	—	—	2	—	—	2
T3	5	3	7	2	2	19
T4	4	3	2	—	—	9
Total	9	6	11	2	2	30

IV cases, the incidences of local recurrence were low, i.e. 27.3% (3 cases) and 25% (1 case), respectively. In contrast, in the 9 Grade I cases and the 6 Grade IIa cases, the incidences were higher, i. e. 44.4% (4 cases) and 50% (3 cases), respectively.

The appearance of regional lymph node metastases before or after the initial treatment was noted in 5 (55.6%) of the 9 T4 patients, but the frequency was somewhat lower in the 19 T3 patients, i.e. 26.3% (5 cases). When the regional lymph node metastases were examined according to the direction of primary tumor extension, the metastases occurred in 2 (33.3%) of the 6 cases of the superolateral type and in 4 (28.6%) of the 14 cases of the inferolateral type. However, the infero- and superomedial types showed a high incidence of regional lymph node metastasis, i.e. in 4 (66.7%) of the 6 patients (Table 5). Secondary metastases to the region of the neck dissection were found frequently in regional lymph nodes in areas such as the parapharyngeal, retropharyngeal and parotid spaces. The regional lymph node metastases after the initial treatment appeared on average 6.8 months later.

When distant metastases were examined in relation to tumor size, the metas-

Table 5 Number of nodal metastases according to T-classification and direction of primary tumor extension

Primary tumor	Direction of primary tumor extension						Total
	Infero-lateral	Supero-lateral	Infero-medial	Supero-medial	Anterior	Posterior	
T2	0/ 1	—	—	—	—	0/1	0/ 2
T3	2/11	0/1	3/5	—	0/2	—	5/19
T4	2/ 2	2/5	—	1/1	—	0/1	5/ 9
Total	4/14	2/6	3/5	1/1	0/2	0/2	10/30

tases occurred in 5 (66.6%) of the 9 T4 patients. This incidence was higher than that for T2 and T3 patients, i.e. 4 (19%) of 21 (Table 6). In all of the 9 patients who developed distant metastases, the lungs were found by clinical examination to be the site of involvement. The metastases were detected after an average of 1 year and 11 months. In 6 of the patients, the metastases occurred after the control of local recurrence and/or lymph node metastases.

The cumulative 5- and 10-year survivals for the 30 treated patients as determined by the Kaplan-Meier method were 72.2% and 65.8%, respectively, for Stage III patients, whereas the number of survivals was apparently decreased (22.5%) for Stage IV patients (Fig. 1). When the cumulative 5-year survivals were examined in relation to the direction of primary tumor extension, the rates were 57.1% and 66.7% for the inferolateral and medial types, respectively. In contrast, the rate was

Table 6 Number of distant metastases according to T-classification and direction of primary tumor extension

Primary tumor	Direction of primary tumor extension						Total
	Infero-lateral	Supero-lateral	Infero-medial	Supero-medial	Anterior	Posterior	
T2	0/ 1	—	—	—	—	0/1	0/ 2
T3	2/11	0/1	2/5	—	0/2	—	4/19
T4	2/ 2	2/5	—	0/1	—	1/1	5/ 9
Total	2/14	2/6	2/5	0/1	0/2	1/2	9/30

apparently lower (20.8%) for the superolateral type. Fourteen of the 30 patients died; 6 from distant metastases, 4 from metastases to regional lymph nodes, 2 from the primary lesions and 2 from other diseases.

Fig. 1 Ten-year cumulative survival rate of 30 patients with maxillary sinus cancers after surgery combined with preoperative chemo- and radiotherapy

Discussion

Patients with maxillary sinus cancer often consult oral surgeons with a complaint of swelling of the alveolar ridge of the upper jaw, associated with pain or ill-fitting dentures. The patients we encountered at our clinic were characterized by an extremely low percentage of early-stage cancer such as T2, and a very high percentage of advanced cancer such as T3 and T4.

During chemo- and radiotherapy, we encountered side effects such as stomatitis and leukopenia, which were exacerbated as the doses of antitumor drugs and irradiation were increased, thus delaying the time of surgical intervention. It has been reported that advanced paranasal sinus tumors respond satisfactorily to combined superselective intra-arterial and systemic chemotherapy, in fact significantly better than reported previously^[12]. When the doses of preoperative

antitumor drugs and irradiation were increased for extensive tumors, the effect was observed histopathologically in the form of an improvement in grade from Grade I to IV^[11]. However, it was difficult to assess the propriety of the dose levels used for chemo- and radiotherapy and to estimate the difference in therapeutic effect between the intraarterial and intravenous routes because of the limited number of patients examined. It was found that the larger the primary tumors were, the lower the histopathological effect of preoperative chemo- and radiotherapy as assessed in terms of Shimamoto's criteria^[11]. When advanced tumors which had destroyed the lateral wall of the maxillary sinus were beyond the area of blood supply originating from the superficial temporal artery, the effect resulting from perfusion of the antitumor drug was not always sufficient. This suggests that there is a limit to the effect of this preoperative combination therapy for the control of extensive tumors. Since tumors of the superolateral type in T4 patients extended to the temporal region, recurrences were often found to appear from the lateral orbital wall to the temporal area. More extensive additional excision was required for wider-reaching tumors of this superolateral^[13], involving a surgical approach not only via a nasolateral skin incision but also via a temporal one.

Local control of T3 tumors by surgery following chemo- and radiotherapy was carried out in 16 (84.2%) of the 19 patients, producing satisfactory results. The cumulative 5-year survival for the 18 patients at Stage III was also high (72.2%). In these patients, dentures were fitted 2-3 months after surgery because disturbance of mouth opening due to postoperative scar contracture was less marked, and facial contour and function were preserved even after 10 years. Therefore, this combination therapy involving surgery after chemo- and radiotherapy is considered to be indicated for T3 patients. On the other hand, T4 patients did not respond well to the combination of intraarterial chemotherapy and radiotherapy. This probably accounted for the viable tumor cells remaining even after surgery. A poorer response of T4 tumors compared with T3 tumors to treatment has been reported in the literature^[4,14,15]. Secondary reconstruction using a deltopectoral flap was performed on patients with facial skin defects resulting from extensive excision of recurrent tumors. In such cases, immediate reconstruction may produce a better result than secondary reconstruction^[16].

In the T3 and T4 patients with tumors of the inferolateral and inferomedial types, lymph node metastases or tumor recurrence in the parapharyngeal or retropharyngeal space appeared frequently after the initial treatment. Therefore, when tumor invasion in these regions is suspected, it is advisable to carry out CT and MRI examinations prior to surgery and excise the lesion *en bloc* through neck dissection including these spaces at the time of excision of the primary tumor. Of the 9 patients who developed distant metastases, one did so after local recurrence of the tumor, 3 after metastases to the cervical lymph nodes and 3 after both local recurrence and metastases. Thus, distant metastases appeared most frequently after tumor recurrence or metastasis to the neck. Metastatic foci in the lung were managed by various modes of chemo- and radiotherapy, but all of the patients died after 1-2 years. Multidisciplinary treatment with incorporation of imaging diagnostic examination, neo-adjuvant or adjuvant chemo- and radiotherapy, and im-

munotherapy has been reported to be useful in patients with advanced cancers^[7,8,17]. Regular follow-up during these periods was very important for early detection and control of recurrent and metastatic tumors.

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