RETROSPECTIVE ANALYSIS OF MULTIDISCIPLINARY THERAPY FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE MAXILLARY SINUS

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Abstract: Purpose: To retrospectively investigate the efficacy of multidisciplinary therapy (concomitant radiotherapy and intra-arterial infusion of 5-fluorouracil (5-FU) followed by maxillectomy) in the treatment of squamous cell carcinoma of the maxillary sinus.

Materials and Methods: We reviewed 71 patient records with locally advanced but resectable carcinoma of the maxillary sinus treated by means of multidisciplinary therapy between 1978 through 1997. The clinical T factor for these patients, according to the UICC definitions (1997), was 12 for T2, 46 for T3, and 13 for T4. Twelve patients were diagnosed as node-positive at initial presentation. Intra-arterial 5-FU was delivered via a superficial temporal artery in accordance with radiotherapy, and the cumulative 5-FU dose ranged from 2,900 mg to 5,250 mg (median 5,000 mg). The total radiotherapy dose ranged from 29 Gy to 48 Gy (median 48 Gy) with conventional fractionation. Patients underwent radical maxillectomy thereafter.

Results: The 5-year overall survival rate and disease-specific survival rate of all the patients were 58% and 68%, respectively. There was no significant correlation of clinical T factor or N factor with disease-specific survival on univariate and multivariate analysis. The overall treatment-related mortality rate was 3.7%. Radiation cataract later developed in all evaluable patients whose lenses were within the treatment volume.

Conclusions: About a half of the operable T4 patients survived over 5 years by means of the above-mentioned multidisciplinary therapy. This multidisciplinary therapy should be compared to treatment with a combination of surgery and postoperative chemoradiotherapy.

Key words: Maxillary sinus carcinoma, Intra-arterial chemotherapy, Radiation therapy, Surgery

INTRODUCTION

Maxillary sinus tumor is one of the more common H&N malignancies among the Japanese population, and 230 deaths occurred from paranasal sinus neoplasms including squamous cell carcinoma of the maxillary sinus in 19971. Because of the sparse lymphatics of the paranasal sinus, this carcinoma seldom develops regional node metastasis unless the tumor extends to areas containing an abundant supply of capillary lymphatics such as the nasopharynx, buccal mucosa, nasal cavity, or skin. Distant metastasis is also very rare and usually emerges as distant failure after initial treatment. Therefore, local control is paramount for prolonged survival in many cases.

The standard treatment strategy for carcinoma of the maxillary sinus has been surgery with radiotherapy in resectable cases, affording 5-year survival rates of 15-40%2,3). However, the sequence of surgery and radiotherapy, the extent of surgical removal (curettage or maxillectomy), the optimal radiotherapy dose and fractionation pattern, and the role of chemotherapy are all still under discussion in the absence of properly designed clinical trials with a sufficiently large patient population. At Asahikawa Medical College Hospital, the standard treatment strategy for patients with resectable maxillary sinus carcinoma has been multidisciplinary treatment composed of i) pathologic diagnosis and tumor debulking by a Caldwell-Luc approach, ii) concomitant intra-arterial chemotherapy (IAC) and radiotherapy, and iii) partial or total maxillectomy. Here we sought to clarify factors affecting the survival of patients bearing locally advanced but resectable maxillary sinus carcinomas treated at a single institution in a consistent manner.

MATERIALS AND METHODS

From September 1978 to June 1997, 106 patients were pathologically proved to have primary squamous cell carcinoma or its variant of the maxillary sinus, and received initial treatment at Asahikawa Medical College Hospital. Of these, 35 patients were excluded from the analysis for the following reasons: distant metastases at diagnosis (two patients), simultaneous other malignancy (two patients), poor status or advanced age and contraindication for multidisciplinary therapy (fifteen patients), omission of concomitant IAC for medical reasons (ten patients), postoperative radiotherapy (two patients), or lost to follow-up within a year after maxillectomy (four patients, who were all free from recurrence at the date of latest follow-up). After
the exclusions, remaining 71 patients were considered for evaluation in this analysis. All of these patients were admitted at the Department of Otolaryngology or Oral/Maxillofacial Surgery of Asahikawa Medical University Hospital by the time of debulking surgery. The group consisted of 49 men and 22 women. Age ranged from 34 to 86 years with a median of 60 years. The tumors were classified as clinical stage II (11 patients, 15.5%), III (39 patients, 54.9%), and IV without distant metastasis (21 patients, 29.6%) (Table 1). There were no T1 or N3 patients in this study population. The involved sites of T4 patients were the orbital contents in 12, cranial base in 1, pterygomaxillary fossa in 7, and sphenoid or posterior ethmoid sinus in 7. Because we reviewed the data on the basis of “intent to treat,” two patients who had developed pneumonitis during chemoradiotherapy were included in the analysis though they did not undergo maxillectomy. Informed consent was obtained in an oral manner from patients or, when this was considered inappropriate, from their family.

1. Clinical evaluation
The routine staging workup consisted of close physical examination by radiation oncologists and either otolaryngologists or maxillofacial surgeons, laboratory examination, complete blood count, blood chemicals, a series of plain radiographs of the cranial base and facial bony structures, and plain chest films. Computed tomography (CT) images were also used for the evaluation of the extent of the primary tumor as well as cervical node status in all but the earliest six patients. Magnetic resonance (MR) images were not available among this study population except for the most recent 3 patients. After these non-invasive examinations, every patient had debulking surgery with pathological confirmation through the gingivobuccal sulcus under general anesthesia, and they simultaneously had percutaneous catheterization into the superficial temporal artery for the purpose of IAC using the technique described by Oberfield et al. By means of dye injection, we confirmed that the catheter tip was placed at the proper position during surgical intervention. All patients were re-staged according to the 1997 UICC system. Clinical stages were invariably applied as a basis for further analysis to avoid stage migration after chemoradiotherapy.

2. Histopathology
Of the 71 study patients, 69 had squamous cell carcinoma and 2 had adenosquamous cell carcinoma. We excluded any adenocarcinoma cases in this study because the clinical behavior of adenocarcinomas might be somewhat different from that of squamous cell carcinomas.

3. Therapy and follow-up
Sixty-five of 71 patients were treated with cobalt telegraphy, while others were treated on a 10-MV or 4-MV linear accelerator. Basically, radiotherapy was delivered using a combination of an orthogonal anterior and a lateral portal with wedges (wedged pair technique) to achieve satisfactory dose distribution. The planning target volume around the gross tumor volume varied from patient to patient, and was determined according to the physician’s speculation about the possible extent of the microscopic tumor. Radiation doses were described as the 90% peak dose at the isocenter plane until 1994 and as the isocentric dose thereafter. CT-aided electron density correction was applied for dose calculation from 1995, while three-dimensional radiotherapy treatment planning was not implemented for any patients in this study. Radiotherapy was delivered four or five days per week. All patients had an intra-arterial infusion of 5-fluorouracil (5-FU) on the day of each radiotherapy treatment. The 5-FU was administered for about 30 min. using an infusion pump one hour before irradiation. Intended total irradiation dose to the reference point was 48 Gy/20 f for earlier 69 patients, and 50 Gy/25 f for the other 2 patients. Intended cumulative 5-FU dose was 5,000mg in 20 to 25 fractions.
Curative surgery (partial or total maxillectomy) by means of en-bloc removal of the maxilla was performed 2-4 weeks after chemoradiotherapy. The surgical resection area was designed individually according to the extent of pretreatment tumor volume regardless of the response to preceding chemoradiotherapy, and was restricted to minimum invasiveness to preserve normal tissue structure. For example, partial maxillectomy with orbital exenteration was performed without resection of the hard palate in cases where the tumor extended into the orbital contents without invasion to the hard palate. The name of “total” maxillectomy was defined as total removal of the maxillary contents, while “partial” maxillectomy as others. Based on clinical and radiological findings, cervical node metastasis presented in 12 patients (17%) during the staging procedure. One T2N1M0 patient whose resected specimen revealed a close surgical margin received adjuvant radiotherapy (20 Gy/10 f) to the primary tumor bed. There was no consistent policy followed regarding the treatment of cervical node metastasis. Five patients underwent radical neck dissection without irradiation, six underwent preoperative irradiation (45 Gy-48 Gv, median 48 Gy) followed by neck dissection, and one received a split course of definitive radiotherapy (48 Gy/20 f/47 days preoperatively and 19.2 Gy/8 f/12 days postoperatively). No patient underwent elective cervical node irradiation.
Patients were basically followed monthly for a half-year and every three months thereafter. Updated information was also obtained from the patients themselves, their families, or attending physicians by telephone. The latest follow-up was obtained as of December 31, 1997. The median follow-up

<table>
<thead>
<tr>
<th></th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>11 (16%)</td>
<td>34 (48%)</td>
<td>14 (20%)</td>
<td>59 (82%)</td>
</tr>
<tr>
<td>N1</td>
<td>1 (1%)</td>
<td>4 (6%)</td>
<td>5 (7%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>N2</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12 (17%)</td>
<td>40 (56%)</td>
<td>19 (27%)</td>
<td>71 (100%)</td>
</tr>
</tbody>
</table>
Survival and time to failure were calculated from the onset of chemoradiotherapy. Recurrence was determined at the date of tumor progression observed clinically or radiographically, and pathological confirmation was invariably made in cases of local failure. Overall survival (OS) included all deaths from any cause. Disease-specific survival (DSS) was defined as patients who died of maxillary sinus carcinoma or who were not available for follow-up. Relapse-free survival (RFS) was defined as patients without any evidence of residual or recurrent tumor at their latest follow-up. Similarly, locoregionally relapse-free survival (LRFS) was defined as patients without any sign of residual or recurrent tumor above the clavicle. Tumor control duration was compared using the log rank test, and the Kaplan-Meyer method was used to determine the OS, DSS, RFS, and LRFS. Cox regression analysis (the proportional hazard model) was used in a stepwise manner to identify prognostic factors and risks for DSS in multivariate analysis. All p values were two-tailed, and those p<0.05 were considered statistically significant.

RESULTS
Twenty-eight patients relapsed by the end of follow-up. The first sites of failure were equally distributed; local in 12 (18% of 67 patients available for evaluation), nodal in 8 (12%), and distant in 9 (13%). One patient had simultaneous failure at the primary site and the homolateral cervical node. The first site of failure and the contents of salvage therapy are listed in Table 2. Salvage therapy was successful (defined as surviving without evidence of disease for more than two years after failure) only in two cases of local failure and in two cases of nodal failure. Patients with distant failure were conservatively managed, and all died 1-28 months (median 3 months) after failure.

1. Compliance to treatment
Of 71 patients, three did not complete their planned chemoradiotherapy. One patient developed fatal interstitial pneumonitis of an unknown origin in the third week of chemoradiotherapy (cumulative radiation dose and 5-FU dose: 28.8 Gy, 4,750 mg). Another patient suffered from severe mucosal reaction leading to chills and high fever in the fourth week, and further chemoradiotherapy was discontinued (38.4 Gy and 3,375 mg). She recovered later and underwent maxillectomy. The last patient developed liver dysfunction that required medication, and underwent radiotherapy alone thereafter (48 Gy and 2,900 mg). In addition, one patient developed fatal interstitial pneumonitis soon after the completion of chemoradiotherapy (48 Gy and 5,000 mg). Dermatitis and confluent stomatitis were invariably observed within radiation fields but were manageable with medication including narcotics without treatment delay or cessation but for the above-mentioned cases. Life-threatening hematotoxicity (WHO grade 4) was not experienced. As a result, cumulative 5-FU doses ranged from 2,900 mg to 5,250 mg (median 5,000 mg) with intended dose (5,000 mg or over) delivered to 57 (80%) patients. Cumulative radiation doses, fraction numbers, and days were 29-48 Gy (median 48 Gy)/12-20 f (20 0/8-52 days (35 days) with intended cumulative dose (48 Gy or over) delivered to 66 (93%) patients. Overall treatment time (OTT), defined from the onset of radiotherapy to the date of maxillectomy ranged from 41 to 77 days (median 53 days). The treatment interval between the end of radiotherapy and maxillectomy ranged from 10 to 42 days (median 19 days). Sixty-nine patients received planned surgery; 58 partial and 11 total maxillectomies. Of these, 17 patients underwent eyeball extraction. Surgical margin status was pathologically negative in 63, and macroscopically negative (without pathological confirmation) in 6. There was no case of apparent residual disease after surgery. Early complications related to surgery were delayed wound healing which required prolonged hospitalization in three patients, postoperative hepatitis in one, and a fatal brain abscess by cranial base infection in one.

After all, three treatment-related deaths occurred; one interstitial pneumonitis during chemoradiotherapy, another interstitial pneumonitis soon after chemoradiotherapy, and one brain abscess after maxillectomy. Thus, the overall mortality rate was 3.7%.

2. Treatment results
CT-based pre-maxillectomy response as combined results of debulking surgery and chemoradiation was as follows; macroscopic tumor clearance (MC) in 20 cases (28%), macroscopic tumor residue (MR) in 34 (48%), and unknown

<table>
<thead>
<tr>
<th>The first site of failure</th>
<th>Opa</th>
<th>RTb</th>
<th>Salvage therapy</th>
<th>Op+RT</th>
<th>Op+CTc</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Regional node</td>
<td>4</td>
<td></td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>17</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

a Opa: operation, b RT: radiotherapy, c CT: chemotherapy
d One patient had simultaneous local and nodal failure.
or treatment cessation (Others) in 17 (24%). Fig. 3 shows LRFS curves according to pre-maxillectomy response. Five-year LRFS rate was 88% in MC cases, 70% in MR cases, and 54% in others. Though MC cases demonstrated a better locoregional control rate compared to MR cases, three curves did not reach statistical significance \((p=0.11)\). OS and DSS for five years including four lost patients were 58% and 68% (Fig. 1) respectively. Median OS was 7.0 years (95% C.I. 0.4-13.7 years), while DSS did not reach to the median value. RFS and LRFS for five years were 60% and 72% respectively (Fig. 2). With respect to DSS, there was no statistically significant difference among the patients of each T factor (five-year survivals: 83% for T2, 68% for T3, 58% for T4, \(p=0.52\)). Clinical stage was not an indicator of prognosis, either (five-year survivals: 82% for stage II, 69% for stage III, 58% for stage IV, \(p=0.51\)). Patients with cervical node metastasis demonstrated a trend toward improved survival with marginal significance (five-year survivals: 91% for positive node, 63% for negative node, \(p=0.06\)) on univariate analysis. The results of univariate and multivariate analyses including age, clinical T stage, and clinical N stage against DSS are listed in Table 3. There was no independent predictor of improved DSS with statistical significance on either of the two analyses.

3. Late complications

With the exception of patients who underwent orbital exenteration at surgery, who had already had orbital complications at the onset of treatment, or who died or were lost within a year after the onset of therapy, 42 patients were available for evaluation for orbital complication. Of these, 19 (45.2%) later developed homolateral cataracts due to orbital irradiation. Time to development of mature cataract was between 1.9 yr. and 4.9 yr. (median 3.1 yr.). Symptomatic

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Table 3 Univariate and multivariate analysis for disease-specific survival who completed trimodal therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Assigned values</th>
<th>Univariate analysis(^a)</th>
<th>Multivariate analysis(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;65 vs. (\geq)65</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td>T2-3 vs. T4</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td>N0 vs. N1-2</td>
<td>0.06(^a)</td>
<td>0.09(^b)</td>
</tr>
</tbody>
</table>

\(P\) values:

\(a\): log rank analysis. \(b\): proportional hazards model.

\(c\): The survival was better in N1-2 group.
retinopathy was never observed. We could not assess the occurrence of keratopathy, dry eye, or conjunctivitis because of insufficient data accumulation. Contralateral visual complications were not experienced. Some patients needed alteration of their meals to soft food after surgery.

**DISCUSSION**

Early detection of maxillary sinus carcinoma is often difficult, and most patients are referred to the hospital presenting with locally advanced disease with or without cervical node metastasis. In addition to our data about carcinomas of the maxillary sinus (T3 or T4; 83.1%), Alvarez et al.\(^{11}\) reported that 60% of 129 patients with paranasal sinus carcinoma had already reached the advanced stage (T3 or T4) when they were referred for treatment. Locoregional control under organ preservation is challenging in such advanced cases.

In 1970, Sato et al.\(^{12}\) first reported 57 patients with maxillary sinus carcinoma treated with simultaneous intraarterial infusion of 5-FU, radiation therapy, and surgical debridement (so-called original trimodal therapy in Japan). They concluded that resection of the maxilla was unnecessary if daily debridement was performed during irradiation and IAC. Stephens et al.\(^{13}\) further confirmed the effectiveness of IAC by treating 13 patients with T3 or T4 maxillary sinus carcinomas in a small, prospective trial consisting of preoperative intra-arterial infusion of bleomycin and methotrexate followed by high-dose radiation therapy and delayed maxillectomy. They observed that 10 of 13 patients had complete clearance of the tumor at surgical specimen, while local recurrence later developed in only one patient. On the other hand, Nahum\(^{14}\) and Goepfert et al.\(^{15}\) argued against the role of IAC that the blood supply to the superior aspect of the maxillary sinus and orbit arises from the internal carotid artery, and that tumors involving these structures would not likely benefit from IAC of the external carotid system. Shibuya et al.\(^{16}\) further confirmed this speculation by means of angiography and Tc-99m injection. A randomized prospective trial was conducted by Nervi et al.\(^{17}\) to address the effectiveness of IAC in cases of maxillary sinus carcinomas, where they failed to show a statistically significant difference between the two arms.

The aggressiveness of surgical intervention differs considerably among institutions from less invasive approach such as daily curettage with radiotherapy to more aggressive method such as en-bloc maxillectomy with or without cranial base surgery. We have applied en-bloc maxillectomy mainly because of three reasons. First of all, macroscopic total tumor removal by repeated curettage seemed inadequate as the majority of our cases were locally advanced. It is reasonable to suppose that the local control would be hampered in the presence of macroscopic residual disease after such less invasive surgery. Second, the practical skill of curettage depends largely on experience of surgeons and less reproducibility can be expected. Lastly, recent advances in reconstructive surgery after maxillectomy complement the cosmetic or functional impairment to some extent.\(^{18,19}\) Comparable results are reported from some Japanese institutions by combining less invasive surgery and a higher radiation dose. Itami et al.\(^{20}\) reported a 59% 5-year local control rate in 37 patients who mainly underwent conservative surgery and repeated piecemeal debulking in a concurrent manner. Kawashima et al combined debulking surgery and postoperative radiotherapy for 43 maxillary sinus carcinomas, and a obtained a 62% 2-year local control.\(^{21}\) These combinations will preserve a good quality of life and may be a good alternative to our multidisciplinary protocol especially in less advanced cases, but only a well-controlled prospective trial will answer this subtle issue.

Another approach to treating carcinoma of the maxillary sinus is postoperative radiotherapy without chemotherapy. Stavrianos et al.\(^{22}\) reported 57 patients of whom 82% underwent postoperative radiotherapy. Local control was 67% for 5 years, and they concluded that adequate surgical clearance, followed by planned postoperative radiotherapy, is the most effective treatment for malignant disease of the maxillary complex. Roa et al.\(^{23}\) used 3D radiotherapy treatment planning for 24 patients with close margins or residual disease after surgery. None of the five patients irradiated for close surgical margins recurred locally, while three of the 14 with microscopic residual (21%) and four of the five with gross residual (80%) recurred locally. Rosen et al.\(^{24}\) treated 15 stage III-IV paranasal sinus cancer patients with a combination of CDDP and 5-FU based induction chemotherapy followed by standard surgical resection and postoperative concomitant chemoradiotherapy. They achieved excellent results with a 79% 10-year local control, although the number of patients was very small (15 patients). Meanwhile, Svane-Knudsen et al.\(^{25}\) showed similar survival between patients with primary irradiation followed by maxillectomy and those with primary lateral rhinotomy followed by postoperative irradiation among 91 patients treated for sinonasal carcinomas. Taking these data and ours (5-year locoregionally relapse-free survival: 66%) into consideration, we cannot reach a firm conclusion about how we should integrate active agent chemotherapy and radiotherapy into surgical removal, though chemotherapy will pay an important role for an improved local control rate and survival for locally advanced cases.

We experienced 8 of 71 patients (11%) who later developed neck node failure after multidisciplinary therapy, including one simultaneous primary and nodal failure. Recent papers reported the incidence of neck node failure as 10-30% in node-negative patients at initial diagnosis, and some of these recommended prophylactic neck irradiation\(^{26,27}\). Paulino et al.\(^{28}\) reported that cervical node recurrence developed in 11 (29%) of 38 patients without metastasis at initial diagnosis, and they advocated the need for prophylactic neck irradiation based on this data. Isolated neck node recurrence was seen in only four of their patients, however, while others were associated with primary failure or distant metastasis. Moreover, contralateral or bilateral neck node recurrence, which would not have been prevented by ipsilateral neck irradiation, occurred in 2 of these 11 patients. We still continue to recommend no prophylactic nodal treatment for negative node patients.

In contrast to the previously published data\(^{29}\), cervical node
Complications

As expected, all patients available for evaluation whose orbital structure was within the treatment volume later developed cataracts. Although cataracts are successfully managed with lens enucleation, one should take the best possible care not to include orbital contents within the treatment volume unless local control rate is sacrificed or orbital exenteration is unavoidable. Roa et al. discussed the normal tissue-sparing capability of 3-dimensional treatment planning when applied to advanced neoplasms of the paranasal sinuses. They reported a 65% local control rate at 5 years for the adjuvant radiotherapy group, while no blindness related to irradiation was observed. They concluded that cervical nodal status would not influence DSS if the primary lesion was resectable and neck dissection was properly performed. The influence of node positivity at initial presentation on the prognosis will be further analyzed on a multi-institutional basis in a separate paper.

CONCLUSIONS

Despite the presence of locally progressive disease in most patients (stage III to IV; 85%), we achieved 68% of DSS in resectable maxillary sinus carcinoma patients after multidisciplinary therapy. Cervical nodal status at initial diagnosis did not affect DSS. Further prospective analysis in comparison with postoperative radiotherapy with or without chemotherapy is warranted. Computer-aided radiotherapy planning promises to reduce the incidence of visual complications while preserving local control rate and is now our routine practice.

REFERENCES

Multidisciplinary therapy for maxillary carcinoma

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要旨：【目的】上顎洞原発扁平上皮癌に対する放射線治療、5FU剤注、及び上顎摘出術からなる集学的治療の治療成績を後向きに解析した。

【対象と方法】対象は1978年から1997年の間に当院で集学的治療を受けた切除可能上顎洞原発扁平上皮癌71例であり、UICC第五版に基づく分類ではT2 12例、T3 46例、T4 13例である。12例は初診時頸部リンパ節転移陽性と診断されていた。5FUは毎日の放射線治療前に局側頭動脈より剤注し、その総量は2,900 mg-5,250 mg（中央値5,000 mg）であった。一方、放射線治療は原則的に直交二等分に射を行い、その総線量は29-48 Gy（中央値48 Gy）であった。その後根治的な上顎摘出術が行われた。

【結果】Kaplan-Meier法による全体の5年累積生存率、及び原疾生存率はそれぞれ58%、68%であった。治療関連死3例（3.7%）に認められた。発病障害として、照射野に悪性水腫体が含まれた症例では全例に自内障が生じた。

【考察】上記集学的治療によって、T4症例の半数に5年生存が得られた。今後、この集学的治療法と術後放射線化学療法との比較試験が望まれる。