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The End Results of Treatment of Maxillary Cancer Analysed According to Modality of Preoperative Treatments

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The results of preoperative treatment and surgical treatment for 146 patients with squamous cell carcinoma of the maxilla in a period between 1957 and 1970 are presented. The 5-year survival rates in patients treated with preoperative radiotherapy and/or intra-arterial infusion chemotherapy with 5-FU, Mitomycin-C, Toyomycin or Endoxan, and in patients treated by surgery alone are approximately 30%, and there is no significant difference in the survival rate in both groups, but the increase in prolongation of patients' life is achieved by the preoperative combined radio- and chemotherapy.

Bleomycin given intra-arterially and followed by extirpative surgery has a surprisingly remarkable effect on both the improvement of the survival rate and the increase of longevity of patients' life. The 5-year survival rate in Bleomycin treated group is 57.1% which is almost twice as much as the survival rates resulted from the other modalities of treatment. Pathological study of tumor tissue removed at the time of operation revealed the cytological efficacy of each modality of treatments in the decreasing order of the combined radio- and chemotherapy, radiotherapy, Bleomycin infusion treatment and other infusion treatment, although the clinical evidences are not always compatible to the results of this pathological study. Data indicate that the efficacy of preoperative chemotherapy appears to vary with each agent, but Bleomycin is the most effective among those agents.

To estimate the extent of tumor treated preoperatively by any of modalities, one must take into account that the residual tumor cells hidden behind the apparently cured area before planning a surgical procedure.

(Key Words : End Results, Maxillary Cancer, Preoperative Treatment, Radiotherapy and/or Chemotherapy)

INTRODUCTION

The percentage of cures of maxillary cancer has been surprisingly increasing in the past two decades. One of the factors that contribute to increase in curability of this malignant disease is a multiplicity of modality of treatments. Because of the limitation of surgery in the treatment of maxillary cancer, preoperative radiotherapy had widely been employed in the 1950's, then preoperative regional chemotherapy with or without concomitant radiotherapy in the 1960's and combination of surgical procedures, radiotherapy and regional chemotherapy in an adjuctive fashion in the 1970's.

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The purpose of this communication is to evaluate the efficacy of each modality of preoperative treatment of maxillary cancer by comparing the end results of surgical treatment to those of preoperative radiotherapy, regional chemotherapy and preoperative combined modality treatment with regional chemotherapy concomitant with radiotherapy in patients treated in the past eighteen years.

MATERIALS AND METHODS

In a 13-year period between 1957 and 1970, 146 patients with squamous cell carcinoma of the maxilla have been treated for cure but not for palliation in the Department of Otorhinolaryngology, Keio University Hospital and its affiliated hospitals. All of 146 patients were successively followed for more than 5 years to date. The patients were classified into five groups according to modality of treatment:

Group I : 41 patients treated by surgery alone.
Group II : 11 treated by preoperative radiotherapy.
Group III : 42 treated by preoperative intra-arterial infusion of chemotherapeutic agents except Bleomycin (BLM).
Group IV : 24 treated by preoperative radiotherapy concomitant with intra-arterial infusion of chemotherapeutic agents except BLM.
Group V : 28 treated by preoperative intra-arterial infusion of BLM.

The methods of treatment were as follows:

1 Surgical procedures

The operative procedure essentially included (1) total resection of the maxilla (2) total resection of the maxilla and the contiguous structures (3) radical maxillectomy and resection of the contiguous structures with orbital exentration (4) radical maxillectomy with orbital exentration and wide exposure of the dura of the base of the skull.

2 Radiotherapy

Radiotherapy comprised of supervoltage radiation with either Co^{60} or linear accelerator (Linac).A maximum tumor dose was 4, 000 rads at 200 rads daily over a period of three to four weeks. Surgery was performed two weeks after completion of radiotherapy.

3 Regional chemotherapy

Chemotherapeutic agents were given by means of intra-arterial infusion through a polyethylene catheter inserted into the superficial temporal artery and directed to the external carotid artery. These agents included 5-FU 250mg/day, Mitomycin-C (MMC) 2mg/day, Toyomycin 0. 5mg/day, Endoxan 100mg/day and Bleomycin (BLM) 15mg/day, and each was dissolved in 20ml of distilled water and given in single daily dose.

The majority of patients received the infusion by one course of 20 daily administrations of the drug, and extirpative surgery was performed soon after the first course of the infusion was completed if the patients tolerated the infusion treatment well without serious complications.

4 Combination of regional chemotherapy and concomitant radiotherapy

Radiotherapy was administered daily within one hour following the intra-arterial infusion with any one of 5-FU, MMC or Toyomycin in a single daily dose. Dose of radiation was already described in the previous part of this section.

Table 1. The 5-year survival rates according to each modality of treatment

Group	Modality of treatment	No. of pts treated	No. of pts survived	Survival rate
I	Surgery alone	41	13	31.7%
II	Preop. radiotherapy	11	3	27.2%
III	Preop. infusion except BLM	42	15	35.7%
IV	Preop. radiotherapy concomitant with infusion chemotherapy	24	8	33.3%
V	BLM infusion	28	16	57.1%
		146	55	37.7%

Because of the aggravation of adverse effect in this combined treatment compared to the other modalities of treatment, surgery was performed after a 3–week interval following the completion of radio- and chemotherapy.

Beside the clinical studies on efficacy of the various methods of treatment, pathological study was also designed to evaluate the efficacy of preoperative treatment by chemotherapy and/or radiotherapy. Tumor tissues extirpated en bloc during surgery in 57 patients were submitted to the pathological study and a whole removed tissue was processed into large serial sections, and examined under a light microscope. In evaluation of the effect of preoperative treatments, the authors classified the tumor tissue response to treatment according to the classification proposed by Shimosato(11).

RESULTS

The 5–year survival rates in each group of 146 patients are shown in Table 1. Up to date, 55 patients survived for more than five years, thus the over-all survival rate in this series is 37.7%. In 70 patients treated by preoperative regional chemotherapy (Groups III and V), 31 (44.3%) survived and this rate exceeds the survival rates in any of the other groups. The over-all survival rates in the other groups are approximately 30% and there no significant difference between those groups from the statistical point of view. There is a significant difference of survival rates between Group III and V in which patients were treated by preoperative regional chemotherapy with Bleomycin, and the 5–year survival rate in Group V is 57.1% (16/28), while that in Group III is 35.7% (15/42). It is, thus, worthy of notice that in all groups except Group V, the 5–year survival rates drop to little more or less than 30%, and there is no statistical difference in the survival rates between these groups.

The 5–year survival figure in each treatment group in each postoperative year is shown in Fig. 1. The survival rate at the first postoperative year in Group I is 30%, and this survival figure continued for the following four years.

Contrary to this, the survival figures at each postoperative year over a 5–year period in Group II, III and IV are markedly high as compared with that of Group I. However, the over-all survival rates in these groups after 5 years are approximately 30%.

The 5–year survival rate of the BLM treated group (Group V) is 57.1 % (16/28), and this figure also exceeds the survival rate in any of the other groups in each postoperative year after completion of the treatment.

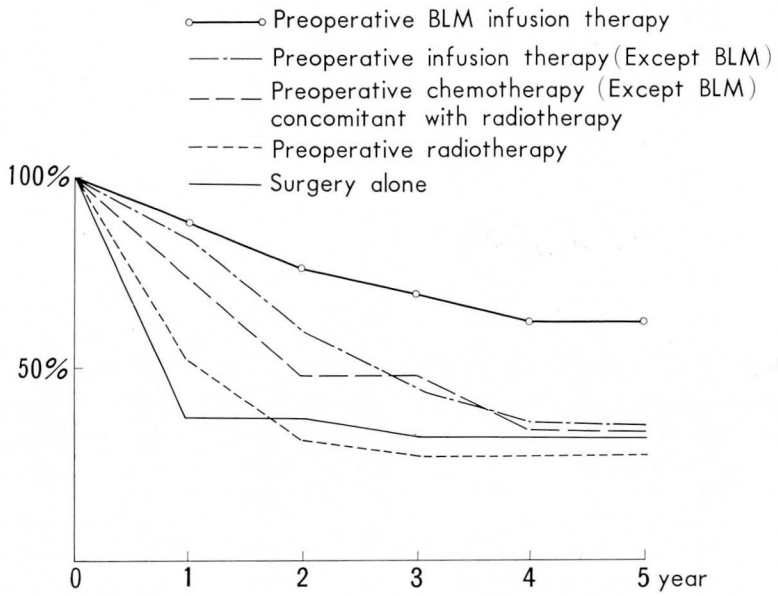

Fig. 1 The Survival Figures according to modalities of treatment.

Table 2. Pathological evaluation of preoperative treatment in 57 maxillary cancers (Squamous cell carcinoma)

	Degree	Irradiation 4500-5000r (9 case)	MMC, Toyomycin infusion (24)	5-FU + Irradiat. (12)	BLM (12)
IV	Complete arrest of tumor	-	-	-	-
III	Low probability of recurrence of tumor	2	1	2	2
IIb	Moderate probability of recur. of tumor	4	2	8	4
IIa	High probability of recur. of tumor	1	4	2	1
I	Inevitable recur. of tumor	2	10	-	1
0	No effect on tumor cells	-	7	-	-

In the results of pathological study of tumor tissue removed from patients treated preoperatively by radiotherapy and/or chemotherapy, the III degree response indicative of regional regression of tumor cell proliferation and low probability of tumor recurrence was found in 22% (2/9) of Group II, 4.1% (1/24) of Group III, 16.6% (2/12) of Group IV and 16.6 % (2/12) of Group V. This result demonstrates no significant difference between the modalities of preoperative treatment. The IV degree response indicative of complete arrest of tumor cell proliferation was not detected in any parts of tumor tissue from any of patients.

The II–b degree response indicative of moderate probability of tumor recurrence was achieved in 44.4% (4/9) of Group II, 8.3% (2/24) of Group III, 66.6% (8/12) of Group IV and 33.3% (4/12) of Group V. The overall effectiveness is shown in Table 2. It is of interest that the results have demonstrated a tumor growth inhibitory effect in the decreas-

ing order of Group IV, II, V and III.

DISCUSSION

As demonstrated by numerous investigations reported previously (1, 2, 4, 5, 6, 12, 14), the 3–year and 5–year survival rates of patients with maxillary cancer were approximately 30% regardless of modality of treatment except BLM. The 3–year and 5–year survival reported by Okuda (6) were 15 % and 6% respectively. Those reported by Kawabe (2) were 23% and 19% respectively. These results indicate that maxillary cancer is still, unfortunately, resistent to treatment. Surgery has reached its limitation of applicability in the treatment of this malignant tumor, and this is assumed by the authors showing the low survival rate in patients treated by surgery alone without preoperative treatments. In 41 patients treated by surgery alone, the 5–year survival rate was 31.5%, and this rate continued from the first postoperative year to the fifth. The authors continued their efforts to break the barrier of this low 30% survival rate, and to improve the prognosis of patients suffering from this resistent and highly malignant tumor, and the treatment of maxillary cancer has been attempted with multidisciplinary approaches requiring surgery, radiotherapy and/or chemotherapy. Okura (7) reported that with preoperative radiotherapy followed by extirpative surgery, both the 3–year and 5–year survival rates were 33 %. Our study also revealed 30% 3–year and 5–year survival rates for preoperative radiotherapy.

After Sullivan (13) reported continuous intra-arterial infusion chemotherapy in 1959, the use of preoperative intra-arterial infusion of anti-cancer chemotherapeutic agents to enhance the survival of patients has been subjected to a clinical trial in our department. Miyake (4) previously roported that intra-arterial infusion therapy with Toyomycin or MMC followed by extirpative surgery for maxillary cancer resulted in a 3–year surviual rate of 40. 4% and a 5–year survival of 26.6%. This effect of preoperative chemotherapy on the survival rate is more strikingly demonstrated when a comparison is made of the 3–year survival curve of resected patients between the group preoperatively treated by chemotherapy and the control group. The 3–year, survival rate was 40. 4% for the preoperatively treated patients and 30% for patients received surgery alone. However, the 5–year follow-up survival rates were almost identical for both the preoperatively treated group and the untreated group. It is of interest to note that when the 5–year survival rate of all patients in this study was compared, the authors find no significant difference between the preoperative chemotherapy groups (Groups III and IV) and the surgery-alone group. However, a major difference was apparent when a comparision was made of the survival rate at each postoperative year over a 5–year period in both groups. The preoperative chemotherapy seems to be capable of prolonging the lives of patients with maxillary cancer. Matsukawa (3), Sakai (8), Satake (9) and Miyake (4) reported a retrospective analysis of the combined modality treatment by intra-arterial infusion with chemotherapeutic agents and concomitant radiotherapy followed by surgery.

Miyake reported that the 3–year survival rate was 38%, and Satake reported the results of 32 patients treated with the intra-arterial infusion with 5–FU and simultaneous radiotherapy, and the 3–year survival rate was 48%

as compared with 26% for patients treated by preoperative radiotherapy or surgery alone. In this present investigation, the 3–year survival rate was 48% and the 5–year survival rate 33% in 21 patients who received combined modality treatment with the intra-arterial infusion chemotherapy except BLM and concomitant radiotherapy followed by surgery (Group IV).

The authors conclude from these data that there is no remarkable difference in the survival rates between patients treated with preoperative intra-arterial infusion chemotherapy except BLM and those treated with preoperative infusion chemotherapy except BLM concomitant with radiotherapy. From the results mentiond above, it is clear that the preoperative chemotherapy except BLM concomitant with radiotherapy increases the longevity of patients to the same extent as preoperative chemotherapy, but no improvement in the 5–year survival rate over that of patients treated only by surgery has been achieved.

Since BLM treatment was introduced for treatment of malignant epitheliomas, this most effective chemotherapeutic agent has been widely accepted in many cancer hospitals and university hospitals in Japan, and what achievement has been made so far in BLM treatment of maxillary cancer ?

In the present study, 28 patients treated with preoperative BLM intra-arterial infusion followed by surgery have been followed up for more than 5 years. Of the 28 patients, 16 (57. 1%) survived more than 5 years without evidence of recurrence of tumor or distant metastases. This 5–year survival rate for BLM treated patients is surprisingly exceed those rate for patients treated by surgery alone or other preoperative combined modality treatments. This result encouraged us to conclude that preoperative BLM treatment followed by surgery has not only increased in prolongation of patients' life but also the improvements in the survival rate of patients with maxillary cancer to levels almost twice as high as the survival rates resulting from other modalities of treatment.

The efficacy of radiotherapy and chemotherapy on tumor growth inhibition has not been well documented in the literature. However, in the present study it is shown that preoperative radiotherapy is efficient in the reduction of viable cell populations in tumor tissue, in contrast with chemotherapy which is less efficient to inhibit the cell proliferation in tumor tissue than radiotherapy. This was demonstrated by the fact that 7 out of 24 specimens from different patients treated by preoperative chemotherapy showed no influence of chemotherapeutic agents to reduce the viable cell population in tumor tissue. It is apparent that this inconsistency in the tumoricidal effects of chemotherapeutic agents is most probably caused by insufficient blood supply to tumor tissue which the agent should reach, and this inconsistency was demonstrated by the findings that there scattered foci of cell necrosis together with foci of the viable cells exhibiting the distinguishing cytologic characteristics in the same specimen. Tumoricidal effects of intra-arterial infusion chemotherapy might be manifested when blood vessels are able to convey the agent to any part of the tumor, while the effect of radiotherapy on tumor is rather indiscriminate. It is attractive to speculate that combining these modalities may theoretically enhance the destruction or control of malignant tumor, although the clinical evidence

is not always compatible with the pathological findings.

Since the failure to cure a malignant tumors by surgical resection is caused by the inability to remove completely all regional extensions of the tumor lesion, or from dissemination of tumor cells, either perior to or at the time of the operation, it has been postulated that the administration of preoperative radiotherapy or chemotherapy, which will render a large percentage of the neoplastic cells incapable of growth or diminish the extent of the lesion capable to be resected, might reduce the incidence of treatment failures. Attempts to make sufficient shrinkage of tumor growth to a resectable size are essential for the treatment of maxillary cancer to eliminate the malignant process completely and to ensure functional restoration as completely as possible, contingent upon circumstances, so that the most satisfactory rehabilitation is effected (10). However, in estimating the extent of tumor and planning the surgical procedure to remove as little tissue as possible, one must take into accout that the residual tumor cells may be hidden behind the apparently curred area where the preoperative treatments are applied.

The use of BLM intra-arterial infusion has yielded the most encouraging experience in the management of maxillary cancer, particulary when its tumoricidal effect is compared with the effects of the other chemotherpeutic agents on tumor cells which is demonstrated by pathological study of the tumor tissue from patients treated preoperatively.

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