Combination therapy for advanced mandibular carcinoma

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Abstract: In the last 3 years, we have performed combination cancer therapy in 7 primary cases of mandibular gingival cancer which involve the lower portion of the mandible by the following regimen: pepleomycin, 5-10 mg intra-arterially (I. A.) or I. V. daily up to a total dose of 30-50 mg, or 5-fluorouracil at 125-250 mg I. A. once daily up to a total of 750-1500 mg', external ^{60}Co radiation at 200 rads once daily up to a total of 1000-1600 rads, for 5-8 preoperative days. From one to five days following this treatment, thorough removal of cancer tissues of the tumorous region was performed in combination with a peroral partial resection; i. e., radical thorough removal of cancer tissues. In all but one case, which was terminated due to another cause, favorable results were achieved so that the shape and function of the mandibular portion of the face was well retained. All patients were rehabilitated orally.

Mandibular gingival cancer is, in most cases, accompanied by invasion and osteoclasia of the mandible. In cases where the invasion and osteoclasia are confined to the alveolar process, marginal resection, chiefly by resection of the alveolar bone, or segmental resection, is the favored surgical technique. However, in cases where the extensive and downward invasion of a tumor is observed in the mandible, the removal of the mandibular quadrant or the continual resection of the mandible has been traditionally indicated. This surgical technique, however, involves problems with regard to the cure rate and the conservation of the mandibular function. Chemotherapy for tumor in the head a neck has been described in a number of reports[1-14]. However, it is considered that there are still problems related to a radical cure of such tumor with chemotherapy.

In recent years, we have used the combination of surgery, radiation therapy and chemotherapy, mainly through a removal of the cancer tissues[15-16], in 7

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cases of mandibular gingival cancer.

The patients recovered from this combination therapy without difficulty and it was possible to favorably maintain their maxillofacial morphology and function. A report on this is presented here.

Cases

Table 1 shows the 7 cases of mandibular gingival cancer which were encountered and treated in the First Department of Oral Surgery, Iwate Medical University Hospital, Morioka, from June, 1977, through January, 1979. These were primary cases with a range in age from 44–75. Six cases were histopathologically defined as squamous cell carcinoma; one, adenocarcinoma ; and all cases were advanced to stage T 4[17]. Fig. 1 presents the intraoral picture on examination of Case 4. Fig. 2 is a panoramic radiograph which reveals that only the inferior border of the mandible is intact. In none of the 6 other cases was the tumor confined to a part of the alveolar process. In each of the other cases, the tumor involved a wide area such as the molar region or the area supplied by the ramus mandibulae and included the adjacent soft tissue. Metastasis to the ipsilateral cervical lymph nodes was noted in 3 cases at the time of the first examination.

Treatment

As shown in Tables Ⅰ and Ⅱ, chemotherapy and radiotherapy were performed only preoperatively; i. e., in 3 cases 5-fluorouracil was administered retrogradely into the superficial temporal artery by a one-shot injectioa at a dosage of 125-250 mg once each day, 5-6 times up to a total dose of 750-1500 mg ; in 2 others pepleomycin sulfate (Nippon Kayaku Co., Tokyo; NK631) was injected

Table Ⅰ

Case, sex & age	TNM classification and histologic diagnosis	Radiation ^{60}Co (ext) rads	Chemotherapy mg	Operation	Prognosis
Case 1; male, 67	$T_4N_3M_0$; squamous cell carcinoma	1,400	Pepleomycin 35, (I.A.)	Radical local cleaning operation + lymph node dissection	NED (No evidence of disease)
Case 2; male, 54	$T_4N_2M_0$; squamous cell carcinoma	1,000	Pepleomycin 50, (I.A.)	Radical local cleaning operation	Terminated fatally from acute renal insufficiency at 10 mos.
Case 3; female, 68	$T_4N_1M_0$; squamous cell carcinoma	1,600	Pepleomycin 40, (I.A.)	Radical local cleaning operation	NED (No evidence of disease)
Case 4; male, 44	$T_4N_2M_0$; adeno-carcinoma	1,200	5-FU 1,500, (I.A.)	Radical local cleaning operation	NED (No evidence of disease)
Case 5; male, 48	$T_4N_3M_0$; squamous cell carcinoma	1,200	5-FU 1,500, (I.A.)	Radical local cleaning operation + lymph node dissection	NED (No evidence of disease)
Case 6; female, 55	$T_4N_1M_0$; squamous cell carcinoma	1,200	5-FU 1,500, (I.A.)	Radical local cleaning operation	NED (No evidence of disease)
Case 7, female, 75	$T_4N_3M_0$; squamous cell carcinoma	1,000	Pepleomycin 30, (I.V.)	Radical local cleaning operation + lymph node dissection	NED (No evidence of disease)

TNM classification: based on the UICC 3rd edition (1978)

Table Ⅱ. Treatment of mandibular gingival cancer

Carcinostatic agent :

Pepleomycin at 5-10mg once a day every day 4-7 times
(by I.A. or I.V. one-shot injection)

or

5-Fluorouracil at 125-250 mg once a day every day 4-7 times
(by I.A. one-shot injection)

in combination with

Radiation :

External ^{60}Co radiation at 200 rads once a day every day 5-8 times

Operation (radical local cleaning operation)

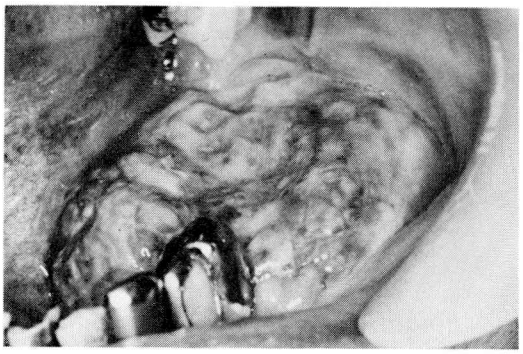

Fig. 1 : An intraoral photograph at the first examination. Mandibular gingival cancer is seen to have grown to involve the area from the left mandibular molar region to the ramus mandibular (Case 4).

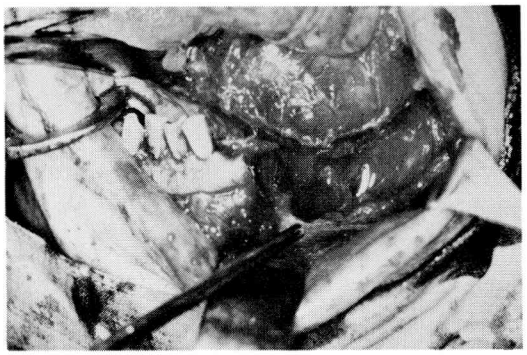

Fig. 3 : On completion of the scheduled simultaneous ^{60}Co radiation to 1200 rads and 5-FU treatment to 1500mg I. A., radical thorough removal of cancer tissues was performed as seen in the photograph (Case 4).

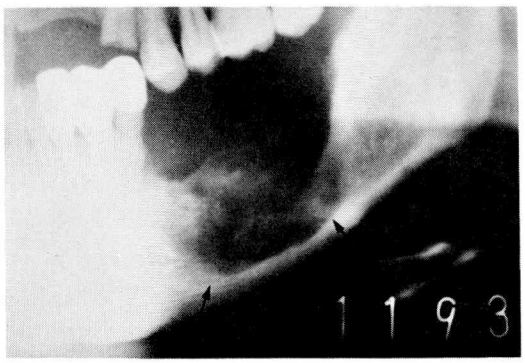

Fig. 2 : A panoramic x-ray film. Severe bone absorption to the arrowed parts due to tumor invasion is seen (Case 4).

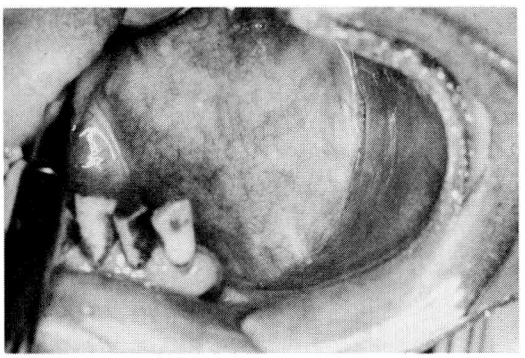

Fig. 4 : A clinical photograph 1 month after the operation in Photo 3. Epithelization is seen to have been completed. Neither cancer chemotherapy nor radiation was performed postoperatively in this case.

at a dosage of 5-10 mg once a day, 4-7 times up to a total dose of 30-50 mg, and in 2 other cases the same agent was administered by I. V. on the same dosage schedule. In all of them external ^{60}Co radiation was performed at a dosage of 200 rads once each day for 5-8 days up to a total dose of 100-1600 rads. By the completion of the radiation schedule the tumor softened and regressed slightly. A radial local cleaning operation, in combination with a partial resection, was performed under general anesthesia 1-2 days later (Fig. 3), at which time the wound was tamponed with a gauze over which 5-fluorouracil ointment was spread for 2-3 days. The site of operation was irrigated and cleaned every day from then on but no postoperative cancer chemotherapy nor radiation was performed. The patients were discharged 1-2 months after the operation when epithelization was complete (Fig. 4).

Metastasis to the cervical lymph nodes was found in 3 of the cases, and lymph node dissection was performed.

Prognosis

As shown in Table 1, Case 2 showed a favorable postoperative recovery course of the operated area but died from acute renal insufficiency at 10 months.

In the other 6 cases, it is now 8 to 29 months after the operations, but no local recurrence nor any metastasis is noted.

The shape (Figs. 5 and 6) and function of the mandibular part of the face is well retained; and the patients have rehabilitated wearing the temporary prosthesis (Fig. 7). In Case 3 absorption of the mandible, due to tumor invasion

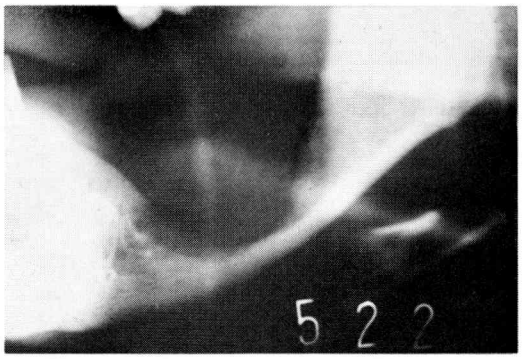

Fig. 5 : A panoramic x-ray film after the operation. The inferior margin of the mandible barely remains, which serves to retain the shape and function of t hemandibular part of the face.

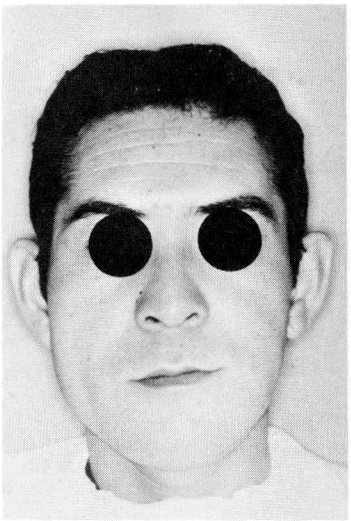

Fig. 6 : Frontal photograph of the head in Case 4 after the operation.

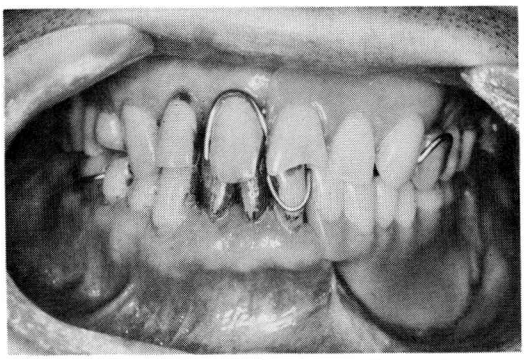

Fig. 7 : Also in Case 4, the patient rehabilitated wearing a temporary prothesis.

involving even the inferior margin of the mandible, was discovered. After the operation, the stump healed to form a false joint, and the mastication function was restored by letting the patient wear a ptothesis, with which he is satisfied.

Discussion

In reference to malignant tumors of the oral cavity, mandibular cancer is often studied as a gingival cancer together with maxillary gingival cancer[18-23]. From the viewpoint that the maxilla differs in anatomical features from the mandible, we studied mandibular gingival cancer without reference to maxillary cancer. Preference for radiotherapy or surgery or combination therapy by these 2 therapeutic means for mandibular gingival cancer has been discussed[19-21]. Today. when both of the therapeutic means have made progress, and the results of these treatments have greatly improved, there remain only a few problems as to their application in the cases of early gingival cancer, while the therapy for advanced cases still involves serious problems as to recurrence and metastasis, and retention of the shape and function of the mandibular part of the face.

In recent years, we have obtained favorable results even in such advanced cases, and the therapeutic regimen is discussed below.

Combination therapy

Chemotherapy: In all cases the anticancer drugs were administered at the same time as radiotherapy, though only in the preoperative stage. The anticancer drugs were pepleomycin and 5-fluorouracil. These were used until the tumor had softened and tended to regress slightly. However, because these drugs were used only up to 1/3-1/5 their usual total doses, no systemic adverse reactions developed nor did any marked abnormality appear in the laboratory findings.
Moreover, the drugs even though used at such low dosages, seemed to have exerted a synergistic effect when applied simultaneously with radiotherapy[24-29].

Radiotherapy : In all cases radiotherapy was also performed only preoperatively by external ^{60}Co radiation 30 minutes after administration of either anticancer drug. It was continued up to a total dose of 1000-1600 rads, which was determined by the severity of the tumor and the area involved. This therapy seemed to eliminate the risk of causin the untoward complication of osteoradionecrosis[30, 31], and because of its low dosages, the wound was rapidly epithelized. According to findings by operaiton, the total dose at which the normal tissue and the tumor could be easily separated and distinguished from each other seemed to be about 1200 rads.

Radical thorough removal of cancer tissues: By this surgical technique we thoroughly curetted the tumor which was detectable by examination and palpation, with a sharp spoon or by removal with a forceps. We smoothed the coarse surface of the absorbed bone and the softened bone, where the tumor was located, with a bone bar. This was for the purpose of cleaning the affected area thoroughly for the combined purpose of performing a partial resection until the normal tissue was confirmed to be exposed.

This procedure can be accomplished perorally by advancing the operation site slowly toward the adjacent involved area away from the tumor center, which barely allows the tumor to remain unremoved and which, providing an open wound, allows ample postoperative obsevation. Even if recurrence might be found during the observation period, the site of recurrence could by operated on by the secondary thorough removal of cancer tissues.

In the cases suspected of metastasis to the regional lymph nodes, curative mandibulectomy should be performed on the primary lesion, and the operation for the metastasis should not be a mere resection of clinically palpable masses but should involve prophylactive extensive dissection of the cervical nodes. However, according to kudo et al.[15], in our department, the control of the primary lesion allowed metastasis to the cervical lymph nodes to grow very little, and today, only excision of the involved lymph nodes without dissection of all cervical nodes suffices for favorable prognosis. Metastasis to the cervical lymph nodes were noted in 3 of the 7 cases of mandibular gingival cancer probably because they were all advanced cases. In all of them only the involved lymph nodes were excised. This has resulted in the control of the primary lesion and also in a favorable prognosis without recurrence. No remote metastasis were found in any of the 7 cases.

CONCLUSION

We have performed triple combination therapy, chiefly by means of radical thorough removal of cancer tissues, in 7 cases of advanced mandibular gingival cancer, and our findings concerning these have been briefly described above.

1. In 6 of the 7 cases, excluding case 1 which died from renal insufficiency, local cancer lesion was well controlled for 8-29 months after their operations, with neither recurrence nor metastasis observed.

2. This combination therapy, featuring radical thorough removal of cancer tissues, is composed of simultaneous chemotherapy and radiotherapy only in the preoperative stage, and this regimen allowed the doses of the 2 therapeutic means to be reduced, which resulted in no development of systemic adverse reactions and in an early, definite epithelization of the surgical wound.

3. This therapy allows the shape and function of the mandibular part of the face to be retained, leading to early rehabilitation of the patient.

内容自抄 最近3年間に顎骨内まで浸潤した下顎歯肉癌（一次症例）の7症例に対し，術前にNK—631を1回5～10mg，計30～50mgまたは5—FUを1回125～250mg，計750～1,500mg動脈内注射あるいは静注し同時に^{60}Co外部照射を1回200rad，計1,000～1,600rad照射併用しこれを5～8回連日実施した。手術はこの1～2日後に口腔内より部分切除を兼ねた局所清掃，すなわち根治的局所清掃術を施行した結果，他病因死した1例を除き良好な治療経過を得ているのみでなく，顎顔面の形態と機能をも良く保存できるようになり，これまでの経過観察期間は短かいが，治療法を中心に検討した。

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