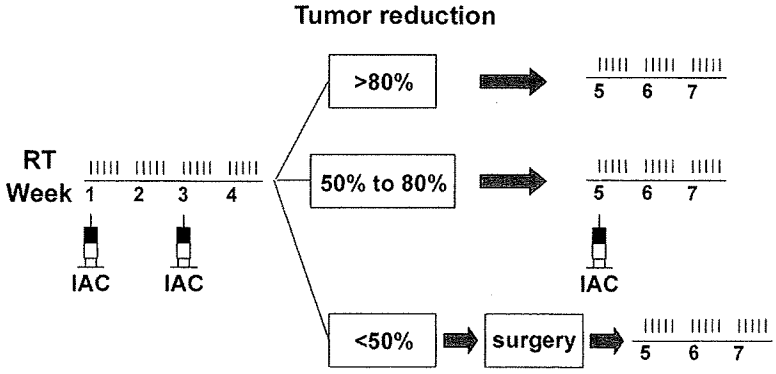

Fig 1. Schematic representation of treatment course. RT — radiotherapy; IAC — intra-arterial chemotherapy; vertical bar — 2 Gy irradiation.

a computed tomography (CT) scan. Those who did not achieve more than 50% tumor reduction underwent surgery at this time point. The patients who showed more than 80% tumor reduction at a dose of 40 Gy received an additional 26-Gy second-phase irradiation without SSIAC. The patients with 50% to 80% tumor reduction received an additional 26 Gy second-phase irradiation with boost SSIAC. The patients with stage III or IV disease were treated with a comprehensive lateral large field radiotherapy portal aimed at all areas affected by the gross disease (primary and nodal) or at risk for subclinical disease extension (eg, uninvolved upper neck), with a cumulative dose of 30 Gy during the second-phase irradiation. At the start of week 1 and week 3, SSIAC and intravenous sodium thiosulfate were administered by an interventional radiologist. After transfemoral carotid arteriography for the assessment of blood supply to the tumor, the contribution of each vessel in supplying blood to the primary tumor was determined with real-time angio-CT. If the blood flow was totally or nearly totally supplied by a single vessel, 100 mg of cisplatin was administered through the artery. For tumors whose blood was supplied by 2 or 3 vessels, the cisplatin was distributed to each artery according to its contribution to the tumor perfusion. One hundred milligrams of cisplatin was infused to the primary site at a speed of 5 mg/min via a 4F microcatheter — a speed slower than the RADPLAT protocol — to reduce the backflow of the infused drugs and to avoid delivery of high concentrations of the anticancer drugs to the eye and the central nervous system via the internal carotid artery. Additional cisplatin (50 mg) was intra-arterially infused to lymph nodes that were larger than 3 cm in diameter. To protect the vascular endothelial cells from the acidic cisplatin solution (pH 2 to 3), we mixed 1.5 mL of 7% sodium hydrocarbonate solution (wt/vol) with 50 mg of cisplatin immediately before infusion.

Simultaneously with the intra-arterial infusion of cisplatin, 14 g of sodium thiosulfate dissolved in Ringer solution, followed by the same amount of sodium thiosulfate, was delivered over a 4-hour period.

Four milligrams of dexamethasone (Decadron; Merck & Co, Whitehouse Station, New Jersey) was also administered to each artery after cisplatin. One milligram of Lamosetrone (Nasea; Astellas, Tokyo, Japan) was administered every 12 hours for 2 days. Two liters of normal saline solution were also administered as pretreatment and posttreatment hydration therapy.

Response Assessment. The tumor response was classified according to the World Health Organization criteria: a complete response was defined as the disappearance of all tumor lesions for more than 4 weeks, and a partial response as a 50% reduction in the product of the perpendicular tumor diameters without the appearance of new metastasis for more than 4 weeks. All patients were evaluated by endoscopic examination, CT, and/or magnetic resonance imaging 4 weeks after the completion of the protocol therapy. The patients were then followed up every month for 2 years, and then every 3 months for at least another 3 years. Salvage surgery was planned for patients with evidence of pathologically persistent disease at the primary site. The patients with suspected residual nodal disease were carefully observed, and those with progressive nodal disease or persistent disease longer than 6 months as depicted by CT underwent neck dissection.

Toxicity Assessment. Acute toxicity, as measured by a complete blood cell count and serum chemistry profile, was assessed weekly during the course of chemoradiotherapy. The toxicity assessments were performed according to the criteria defined by the Common Terminology Criteria for Adverse Events version 3.0 of the National Cancer Institute.

Statistical Analysis. The aim of this study was to the determine response rate, locoregional control rate, survival rates, and toxicity associated with the Kanazawa regimen and to compare the results to those of the multi-RADPLAT. The overall surviv-

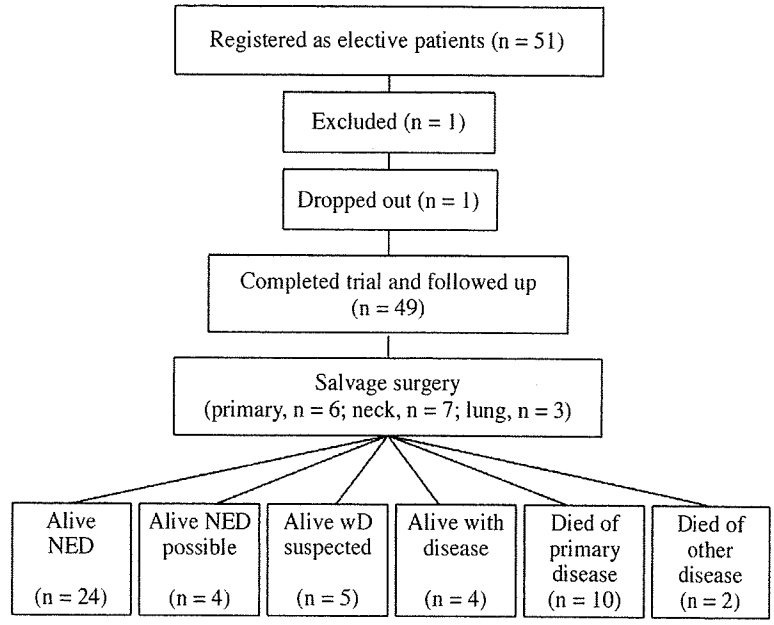

Fig 2. Diagram of clinical course in 51 registered patients. Alive NED — alive with no evidence of disease, meaning progression-free survivors; Alive NED possible — alive with no evidence of disease longer than 2 years after salvage surgery; Alive wD suspected — alive with no evidence of disease less than 2 years after salvage surgery.

al rate, progression-free survival rate, local control rate, and locoregional control rate were analyzed by the Kaplan-Meier method, and the differences between the curves were analyzed by the log-rank test. The time to an event was calculated from the start of the treatment.

RESULTS

Feasibility. Figure 2 details the treatment results of this study. From December 1998 to March 2003, 51 patients were recruited for this study. One patient was excluded because he had hereditary anemia. One patient was included in the dropout group as the patient rejected the treatment after the first course of chemotherapy. As a result, 49 patients completed this regimen (feasibility, 98%). All living patients had a minimum follow-up period of 2 years (range, 3 to 76 months; median, 32 months; Fig 2).

Received SSIAC and Response. Eleven patients received SSIAC twice, and 33 patients received 3 cycles of SSIAC. Thirty-nine patients (80%) and 5 patients (10%) achieved complete and partial responses, respectively, at the primary and involved lymph nodes. Five of 5 patients with stage II disease had 2 cycles of SSIAC and achieved a complete response. Five patients underwent operation after 2 courses of SSIAC plus 40 Gy of irradiation; 4 of these 5 patients had stage IV disease. Six patients with a nodal metastasis larger than 3 cm in diameter received an additional cisplatin infusion. One patient had a persistent neck mass, and the other 5 patients had a complete clinical response (Table 2).

TABLE 2. NUMBERS OF DIFFERENT CHEMOTHERAPIES AND RESPONSE RATES

	Stage			
	II	*III*	*IVa*	*Total*
IAC ×2	5	2	4	11
IAC ×3	0	10	23	33
IAC ×2 + surgery	0	1	4	5
Complete response	5	11	23	39
Partial response	0	1	4	5
Surgery	0	1	4	5
Total	5	13	31	49

IAC — intra-arterial chemotherapy.

Survival. Thirty-nine of 49 patients (80%) survived 2 years after the treatment (Fig 3 and Table 3). Twenty-six of 49 patients (53.1%) were alive without disease (Fig 4 and Table 3). Including the 3 patients with salvage surgery, local disease-free control was achieved in 39 patients (80%). For 36 patients (73.5%), a disease-free primary organ was preserved for 2 years after treatment (Fig 5 and Ta-

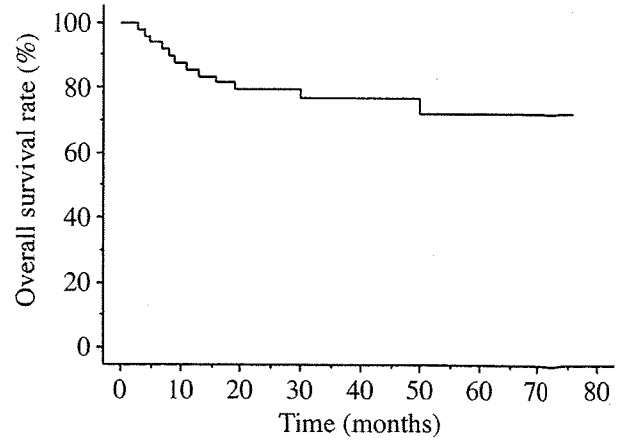

Fig 3. Overall survival.

TABLE 3. SURVIVAL RATES

	Year	No. of Cumulative Deaths	No. of Patients at Risk	Patients Alive* (%)
Overall survival	0	0	49	100
	1	7	42	85.7
	2	10	39	80
	3	11	23	77.6
	4	12	16	75.6
Progression-free survival	0	0	49	100
	1	19	30	61.2
	2	23	26	53.1
	3	24	16	51
	4	25	10	49

*In cases of progression-free survival, alive with no evidence of disease.

ble 4). Locoregional disease-free control for 2 years was obtained in 38 patients (77.6%). Thirty patients achieved locoregional disease-free control for 2 years without salvage surgery (Fig 6 and Table 4).

The patients treated by surgery with 40 Gy irradiation and 2 courses of intra-arterial chemotherapy had a similar overall survival rate in comparison to the patients with a complete response (80% and 84.6%, respectively). However, the patients with a partial response had significantly worse prognoses (40%; Fig 7).

Relapse and Salvage. Ten patients underwent salvage surgery (Fig 2). Of the 7 patients who underwent neck dissection, pathological evidence of neck disease was obtained in 6 specimens; however, 1 patient with a persistent cervical node mass for 6 months did not have any pathological neck metastasis. Of the 5 patients who received an intra-arterial infusion of cisplatin into the cervical lymph node metastasis, only 1 patient had a recurrence at the original node. This patient also had a local recurrence and therefore underwent salvage surgery for

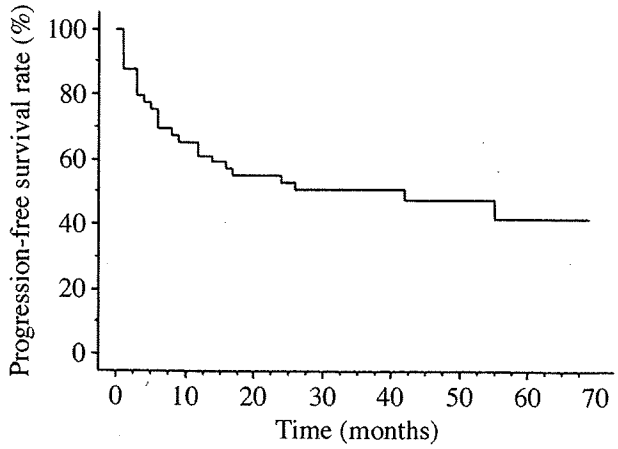

Fig 4. Progression-free survival.

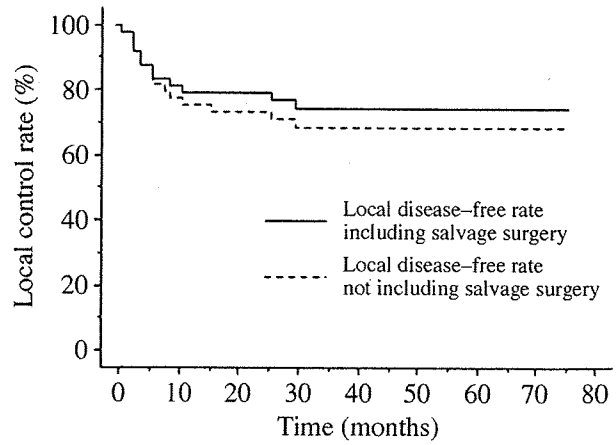

Fig 5. Local tumor control.

local and regional diseases.

Adverse Effects. There were 4 cases of hematologic grade 3, and 7 cases of mucosal grade 3 events. There was 1 case of a grade 4 event. Tissue necrosis (larynx) arose in 1 patient 8 months after the completion of the entire protocol, and was thus considered to be a late toxicity. The patient underwent total laryngectomy. One patient had a subcutaneous hematoma at the puncture site of the femoral artery. The hematoma disappeared without any medical

TABLE 4. ESTIMATION OF LOCAL AND LOCOREGIONAL CONTROL RATES

	Year	No. of Cumulative Failures	No. of Patients at Risk	Control Rate (%)
Local control without surgery	0	0	49	100
	1	12	37	75.5
	2	13	36	73.5
	3	15	21	69.4
	4	15	13	69.4
Local control with surgery	0	0	49	100
	1	10	39	80
	2	10	39	80
	3	12	21	75.5
	4	12	13	75.5
Locoregional control without surgery	0	0	49	100
	1	16	34	67.3
	2	19	32	61.2
	3	21	19	59.2
	4	21	13	59.2
Locoregional control with surgery	0	0	49	100
	1	7	42	85.7
	2	11	38	77.6
	3	12	19	75.5
	4	12	13	75.5

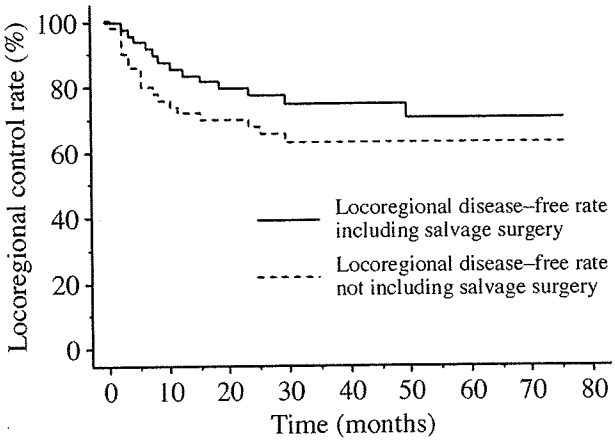

Fig 6. Locoregional tumor control.

treatment. No patient had a catheter-related central nervous system problem or peripheral neuropathy (Table 5).

DISCUSSION

Many studies have supported the remarkable efficacy of the RADPLAT regimen for the local control for advanced HNSCC.[4,13-15] Because the toxicities of cisplatin were considered to be reduced by sodium thiosulfate, we did not change the dose of cisplatin on the basis of body surface area, but used a fixed dose for the body. The effectiveness of concurrent chemoradiotherapy has also been suggested to be predicted by the primary tumor volume and the tumor regression rate.[16,17] Therefore, the required dose of cisplatin for controlling local disease can be determined on the basis of the targeted tumor volume, and the treatment can also be switched from chemoradiation to surgery according to the tumor regression rate. In other words, a larger tumor may be controlled by an increased dose of cisplatin as in the RADPLAT regimen, and moderately large tumors may be controlled by a lower dose of cisplatin

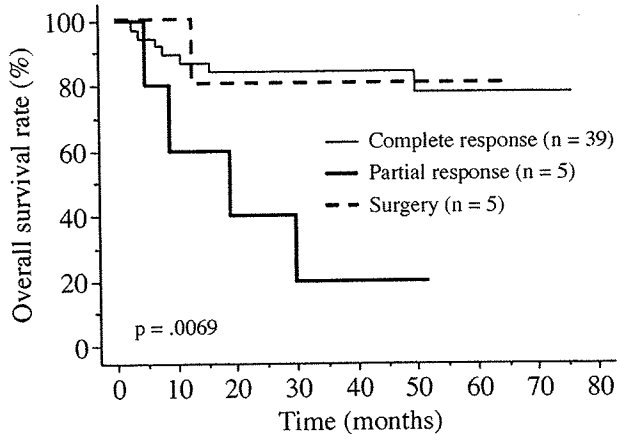

Fig 7. Overall survival of patient cohorts classified with treatment response.

TABLE 5. TOXICITY RATES

Type of Toxicity	Grade 3 No. of Patients	Grade 3 %	Grade 4 No. of Patients	Grade 4 %
Hematologic	4	8.2	0	0
Nonhematologic				
Mucosal	7	14.3	1	2
Central nervous system	0	0	0	0
Infection	0	0	0	0
Overall worst grade of toxicity per patient	13	26.5	1	2

with reduced toxicity. A more detailed study is necessary to determine the optimal dose based on the tumor volume.

The feasibility of the protocol examined herein was therefore found to be better than that of RADPLAT (SSIAC, 97.0%; RADPLAT, 85%). As a result, the first aim of this study, namely, to establish a high-compliance protocol, seems to have been accomplished. The control rate of neck disease was higher than that of Robbins et al.[7,12] However, the overall, local disease-free, and progression-free survival rates did not show a significant difference, and these data concerning survival were comparable with those of RADPLAT. The latest data on RADPLAT include rates of complete response, 2-year survival, 2-year locoregional control, and 2-year disease-free survival of 80%, 63%, 57%, and 46%, respectively.[14] The similarity in efficacy between RADPLAT and the Kanazawa regimen, regardless of the reduced dose and frequency, could be explained by the fact that the proportion of patients with stage IV disease was approximately 75% in the early study and 100% in the latest study of RADPLAT, and the proportion of patients with stage IV disease in this study was only 50%.[4,14]

Of the 22 patients with N2 nodal metastasis, 2 patients with residual or recurrent neck disease underwent neck dissection. However, 6 patients with large nodal metastases who were given an additional cisplatin infusion to their neck disease did not develop nodal recurrence. A planned neck dissection has been recommended for the treatment of N2 or more advanced neck disease.[18,19] However, surgical treatment after concurrent chemoradiation therapy results in severe scar formation and impairs the quality of life. Alternatively, patients with large nodal disease may be able to avoid a planned neck dissection with an additional cisplatin infusion to the advanced neck disease. This hypothesis thus seems worth evaluating in a future study.

Many authors have postulated that local control and survival strongly correlate with the kinetics of

the tumor response. Therefore, patients with faster-responding tumors are expected to have a better prognosis than those with more slowly regressing tumors.[17] Local control is an important prognostic factor for head and neck cancer patients. Therefore, the poor responders with less than 50% regression after 40 Gy irradiation and 2 courses of SSIAC were treated by surgery. The overall survival rate of the poor responders was comparable to that of the patients with a complete response. The prognosis of the poor responders, whose treatment plan was changed to surgery, was significantly better than that of the partial responders, who received full-dose chemoradiotherapy.

The prediction of chemoradiosensitivity is still difficult for heterogeneic malignant tumors, such as HNSCC. Theoretically, from a radiation-oncological viewpoint, establishing a treatment decision point at 40 Gy may be argued. Practically speaking, however, the decision-making criteria in this protocol appear to be satisfactory, because the overall survival rate of patients who underwent surgery after 2 cycles of SSIAC plus 40 Gy of irradiation was comparable to that of the patients with a complete response, and it was also better than that of the patients with a partial response. Alternatively, a more intensive chemoradiotherapy regimen might also have improved their prognosis. However, such treatment always comes with a considerable increase in the associated adverse effects. A boost-accelerated radiotherapy with 4 cycles of SSIAC (cisplatin, 150 mg/m^2) was not feasible because of severe acute toxicity and treatment-related deaths — a finding that suggests the limitations of obtaining an improvement by escalating the treatment intensity in concurrent chemoradiotherapy.[20] Furthermore, severe impairment of the target organ and hematologic toxicity may also cause a delay in surgical treatment, which may worsen the prognosis.

The patients involved in this study had tumors at various sites. We hope that the efficacy of our protocol will be further studied according to both the anatomic site and the tumor volume.

CONCLUSIONS

Although the sample size of this study may not be sufficient for the results to be conclusive, the Kanazawa regimen, which treats patients with a lower dose of cisplatin than does RADPLAT while also treating poor responders with surgery during the chemoradiation course, was considered to be quite effective for the treatment of resectable advanced head and neck cancer, and thus may be the treatment of choice. Moreover, the results of this exploratory study encourage us to plan further clinical studies.

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CASE REPORT

Intra-arterial chemotherapy for laryngeal cancer via a non-bifurcating carotid artery

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ABSTRACT. The common carotid artery (CCA) usually divides into the internal carotid artery (ICA) and the external carotid artery (ECA). We present an extremely rare case of a non-bifurcating carotid artery through which intra-arterial chemotherapy for laryngeal cancer was administered. The CCA angiogram, as well as ultrasonographic evaluation of the carotid arteries, demonstrated a non-bifurcating CCA that subsequently constituted the ICA. Furthermore, several branches normally given off by the ECA arose directly from the single carotid artery. Superselective intra-arterial infusion of *cis*-diamminedichloroplatinum (II) (CDDP) was subsequently performed.

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The common carotid artery (CCA) usually divides into the internal carotid artery (ICA) and the external carotid artery (ECA) at the level of the fourth cervical vertebra or the upper border of the thyroid cartilage. The ECA branches into many arteries after the bifurcation. However, the ICA has no arterial branching in the cervical portion, with the exception of the inferior pharyngeal artery [1]. Multiple anomalies of the carotid artery circulation have been described. Some reports describe an absence of the CCA. In those cases, the ECA and the ICA arise independently from the brachiocephalic artery or the aortic arch. Other reports describe how the ICA supplies a small number of arteries commonly arising from the ECA. However, it is extremely rare for the CCA to ascend in the neck without undergoing bifurcation while supplying multiple branches in the cervical portion [2–4]. We present an extremely rare case of a non-bifurcating carotid artery through which intra-arterial chemotherapy for laryngeal cancer was administered.

Case report

A 64-year-old female patient with a 6-month history of hoarseness was referred to us for evaluation of possible laryngeal tumours. A fibre-optic laryngoscope demonstrated irregular thickening of the surface of the bilateral vocal cords with left side predominance. Mobility of each vocal cord was normal. The surface of the bilateral false vocal cords was clear; however, slight bulging was observed in the anterior portion of the right side. There were no palpable neck nodes. Biopsy was taken under local anaesthesia through a fibre-optic laryngoscope; the pathological diagnosis was moderately differentiated squamous cell carcinoma.

A CT scan with contrast enhancement demonstrated a right supraglottic mass measuring 12 × 8 mm, which extended into the bilateral vocal cords. The mass invaded the right paraglottic space without destruction of the thyroid cartilage. There were no cervical lymph nodes suspected of metastasis. On ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography, intense accumulation was demonstrated, and the standardised uptake value was 13.7 in the right supraglottic lesions extending into the bilateral vocal cords. There were no other abnormal accumulations. Therefore, the patient was diagnosed as having a supraglottic laryngeal cancer of T3N0M0 (Internation Union against Cancer, 2002).

In this case, concurrent chemoradiotherapy was planned and superselective intra-arterial chemotherapy was scheduled. This protocol had been performed for resectable advanced head and neck cancers for several years in this hospital with approval of the institutional review board [5]. On ultrasonographic evaluation of the carotid arteries, the left side, contralateral to the tumour, showed a normal CCA with its bifurcation, the ICA and ECA and its branches. The pulsatility index (PI) was calculated to analyse blood flow definitively. The PIs in the left CCA, ICA and ECA were 1.20, 1.22 and 1.89, respectively. Surprisingly, however, the right ECA was not depicted in the area where the bifurcation of the CCA is usually observed. There were three branches demonstrated from the single carotid artery. The pattern of blood flow in the cephalic portion of the single carotid artery looked like the ICA. The PIs in the right CCA and the cephalic portion of the single carotid artery were 1.23 and 1.04, respectively. Therefore, it was considered that the CCA did not bifurcate, and subsequently constituted

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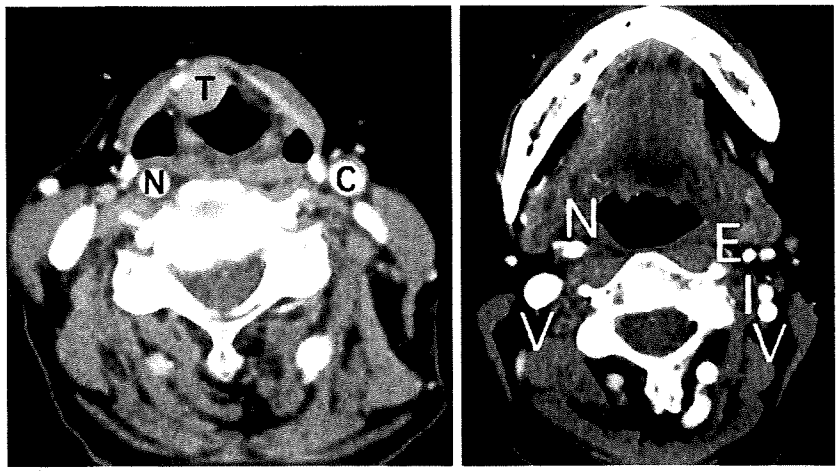


(a) (b)

Figure 1. CT scan with contrast enhancement at (a) the level of the middle of the thyroid cartilage showing a relatively median location of the right non-bifurcating carotid artery (N) compared with that of the left common carotid artery (C), and (b) at the level of the tip of the epiglottis showing the right non-bifurcating carotid artery (N) with a divided branch compared with a division into the internal carotid artery (I) and the external carotid artery (E) on the left side. T, upper part of the supraglottic tumour; V, internal jugular vein.

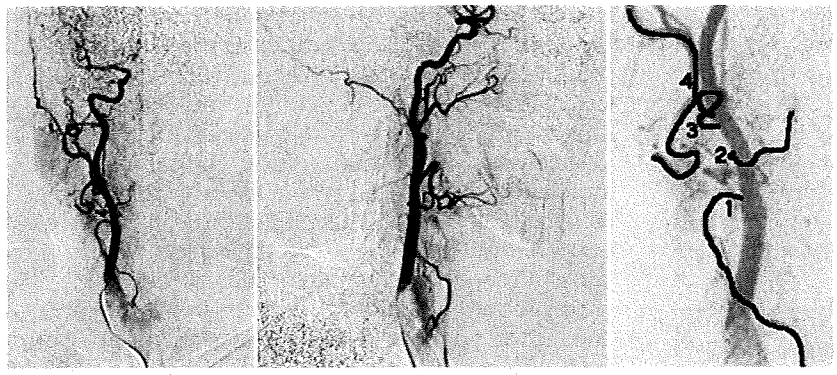
the ICA, with branches normally rising from the ECA. A contrast-enhanced CT scan previously performed also demonstrated a pattern similar to that observed on ultrasonographic studies (Figure 1).

The carotid angiogram was performed through the femoral route. The brachiocephalic artery and divisions of the right subclavian artery and the right CCA looked normal. The right CCA angiogram clearly demonstrated that the CCA did not bifurcate and subsequently constituted the ICA towards the brain (Figure 2). Several branches, such as the superior thyroid artery, lingual artery, facial artery and common trunk of the superficial temporal artery and internal maxillary artery, arose directly from the single carotid artery (Figure 2). A superselctive angiogram of the right lingual artery showed tumour stain, and a CT scan conducted during the angiogram (CTA) demonstrated positive stain within the right supraglottic lesion (Figure 3). Although the position of the catheter after insertion into the targeted artery might have been unstable in previous cases, the catheter was very stable at this time. Therefore, an intra-arterial infusion of *cis*-diamminedichloroplatinum (II) (CDDP) was administered. Similarly, a superselctive right superior thyroid artery angiogram and CTA demonstrated feeding into the lower portion of the tumour, which was followed by an intra-arterial infusion of CDDP. Because the right supraglottic lesion extended into the left vocal cord, a left CCA angiogram was subsequently performed. The superselective left superior thyroid artery angiogram and CTA demonstrated blood supply to the lesion extending into the left side; CDDP was also infused. The left CCA, ICA and ECA and its branches appeared normal. There were no major adverse effects during the procedure.

Discussion

Embryologically, the ICA is formed from the third aortic arch and the dorsal aortic root cranial to it. The ECA arises as a new branch from the ventral aspect of the third aortic arch, and comprises two connected arteries — the ventral pharyngeal artery and the stapedial artery [6]. A capillary network with vascular buds from the neighbouring arteries forms branches of the ECA. Therefore, the superior thyroid artery, the facial artery and the internal maxillary artery are developed from the ventral pharyngeal artery, and the middle meningeal artery is developed from the stapedial artery. Those linkages thus form the ECA.

Two interpretations are possible for this rare case of non-bifurcating carotid artery, as suggested in previous reports. One is agenesis of the main trunk of the ECA [7]. As the new outgrowth from which the ECA will be formed does not arise, all of the branches of the ECA may form connections with vascular buds from the third aortic arch or dorsal aorta. The fact that the trunk has a carotid body, which is almost always located in the ECA, supports this hypothesis. The other interpretation is agenesis of the proximal segment of the ICA [8]. As the



(a) (b) (c)

Figure 2. Right carotid angiogram in the (a) anteroposterior view and (b) lateral view showing the non-bifurcating carotid artery, and (c) an overlapping schematic diagram showing branches of the non-bifurcating carotid artery. 1, Superior thyroid artery; 2, lingual artery; 3, facial artery; 4, common trunk of internal maxillary artery and superficial temporal artery.

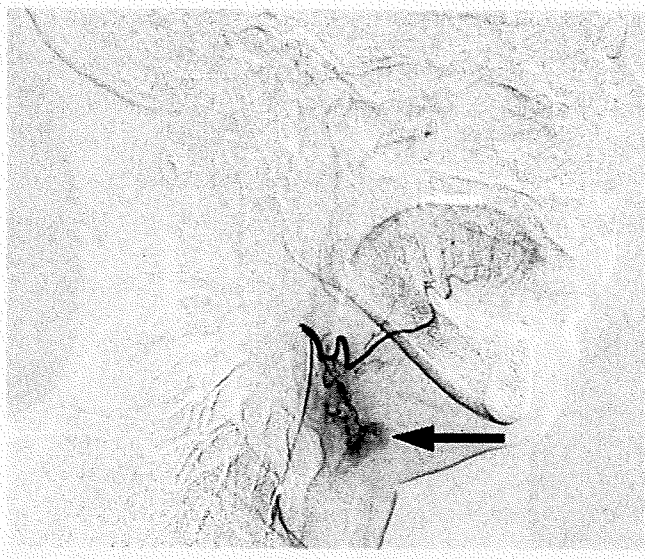


Figure 3. Superselective right lingual artery angiogram showing tumour stain (arrow).

ventral pharyngeal artery and the stapedial artery form the usual ECA without developing a third aortic arch, the ECA connects to the distal portion of the dorsal ventral artery at the level of the first cervical vertebrae (C1). The tortuosity of the non-bifurcating carotid artery at the C1 level, as well as the identification of an arterial stump of the ICA in some cases, supports this hypothesis.

Although the portion of the single carotid artery without branches in this case showed a relatively medial upward course compared with the opposite side (Figure 1, left panel), the location of the portion of the artery with branches was similar to that of the contralateral ECA (Figure 1, right panel). However, in this case, the immediate portion of the superior thyroid artery after division directs laterally, although the artery usually directs anteromedially (Figure 2, right panel). Similarly, although both the facial artery and the lingual artery usually direct medially, those were directed laterally at the immediate portion after division. Therefore, the single carotid artery in this case did not seem to be the ECA. Furthermore, an ultrasonographic study demonstrated that the blood flow pattern of, as well as the PI in, the cephalic portion of the non-bifurcating carotid artery appeared similar to that of the ICA. In addition, there was no apparent tourtuosity of the artery at the C1 level. These findings suggest that this case is in favour of the former interpretation, *i.e.* agenesis of the main trunk of the ECA.

Conclusions

Non-bifurcating carotid artery is an extremely rare condition, and needs to be recognised in the treatment (including intra-arterial chemotherapy) of head and neck cancers. In addition to angiograms, CT scans with contrast enhancement and ultrasonography contributed to the accurate diagnosis of this rare anomaly.

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ORIGINAL ARTICLE

Effects of Japanese herbal medicine, Juzen-taiho-to, in otitis-prone children – a preliminary study

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Abstract

Conclusion: Juzen-taiho-to (JTT, TJ-48), a Japanese herbal medicine that improves immune function, was found to be effective in otitis-prone in children. *Objective:* To evaluate the efficacy of JTT against intractable and recurrent infections in immature immune systems, we administered JTT to otitis-prone infants and investigated clinical changes before and during JTT administration. *Subjects and methods:* Twenty-four otitis-prone infants were administered JTT at 0.10–0.14 g/kg/day twice a day for 3 months. We compared clinical course, such as frequency of acute otitis media (AOM), duration of fever and antibiotics administration, and hospital visits for the periods before and during JTT administration. *Results:* Medication compliance rate was 87.5%, and administration of JTT led to remission in 95.2% patients. No apparent side effects were observed. The frequency of AOM decreased significantly (Wilcoxon signed rank test, $p=0.000$) with JTT. The duration of fever ($p=0.000$) and administration of antibiotics ($p=0.001$), as well as the number of hospital visits ($p=0.001$) and emergent hospital visits ($p=0.000$) showed significant decreases after JTT administration. After the end of the JTT period, 14 of 21 (66.7%) patients started to take it again, as they experienced purulent otitis media and/or other infections after discontinuation. The frequency of AOM increased significantly after stopping JTT ($p=0.004$) and decreased again with JTT resumption ($p=0.005$).

Keywords: *JTT, TJ-48, immune function, drug-resistant bacteria, acute otitis media, immune immaturity*

Introduction

The unique role played by traditional Japanese herbal medicines (Kampo) is gradually attracting worldwide attention. Juzen-taiho-to (JTT, JT-48) is a nourishing agent that is used to improve disturbances and imbalances in homeostasis, and it is known to increase immune function by enhancing phagocytosis [1], cytokine production [2], antibody production [3], and the mitogenic activity of spleen cells [4]. Recent investigations have also reported that JTT has anti-tumor effects, such as suppression of tumor metastasis [5] and prolongation of survival [6], and that it protects against the adverse effects of chemotherapy [7] and radiotherapy [8] by influencing the immune response. JTT has also been reported to have protective effects against Candida albicans infection [9].

Acute otitis media (AOM) is one of the most common diseases in early infancy and childhood. However, some children experience more frequent and recurrent bouts of AOM. The increase in the number of otitis-prone infants and the rapid emergence of drug-resistant bacteria associated with AOM are now generating increasing concern [10–12]. Although antibacterial medication is generally effective against bacterial infection, overuse of antibiotics has led to the increased emergence of drug-resistant bacteria. In addition, otitis-prone patients are sometimes unable to recover from intractable inflammation of the middle ear, which can progress to more serious conditions, such as mastoiditis, meningitis, cerebritis, otitis interna, and sigmoid sinus thrombosis.

Onset and progression of infection are determined by the relative balance between the reproductive

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power of microbes and host defense, and immune immaturity is one of the reasons why the majority of otitis-prone patients are under 3 years of age. It has also been reported that response and development of immune function are poor in otitis-prone children [13–15]. In this study, we investigated the effects of JTT in otitis-prone children.

Subjects and methods

We examined 24 otitis-prone infants who experienced repeated purulent otitis media, despite conventional management. Otitis-prone children were defined as children who had more than three episodes in 6 months, more than four episodes in 1 year, or more than four episodes by the age of 2 years [14]. After obtaining informed consent, JTT at 0.10–0.14 g/kg per day was administered twice a day before milk or food for 3 months. No restrictions were imposed on conventional treatments for otitis media or any other disease while JTT was administered. We investigated the frequency of AOM, duration of fever and antibiotics administration, and number of hospital visits and emergent hospital visits in the periods before and during JTT administration. AOM was diagnosed by otolaryngologists based on examination of general and tympanic findings. Unilateral AOM was counted as a single occurrence, while bilateral AOM simultaneously diagnosed in both ears was counted as two occurrences. Recurrent ear discharge and exacerbation during treatment were regarded as different episodes of AOM. Fever was defined as a body temperature of more than 37.0°C in patients whose normal temperature was under 37.0°C, or as a rise of more than 1°C in patients whose normal temperature was more than 37.0°C. Hospital visits included otolaryngology, pediatrics, and emergency room visits for any reason related to patient conditions. Total hospital visits were counted as 'hospital visits,' and unscheduled hospital visits due to unexpected circumstances, such as sudden fever, infectious symptoms or other diseases, were counted as 'emergent hospital visits.' The number of days before and during administration of JTT was also counted for each patient, and each parameter was calculated as an average number per 30 days (number per month). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and complied with the Helsinki Declaration of 1975, as revised in 1983.

Statistical parameters were ascertained using SPSS software (13.0J for Windows; SPSS Inc., IL, Chicago, USA). The statistical significance of differences between the groups was determined by Wilcoxon signed rank test. $p < 0.05$ was considered significant.

Results

JTT was given to 24 otitis-prone infants (15 males, 9 females; median age at the start of JTT administration, 14 months; range 6–33 months). Observational time before starting JTT administration was 20–214 days (mean $\pm$ SD $= 86.0 \pm 46.7$ days). While three infants were unable to continue taking JTT, 21 infants had no difficulties. The medication compliance rate was 87.5% and no apparent side effects were observed during JTT treatment.

The frequency of AOM decreased significantly (Wilcoxon signed rank test, $p = 0.000$) with oral administration of JTT (Figure 1). Mean and standard deviation of the frequency of AOM before the JTT administration period was 3.41 ± 2.00 (times/month), which decreased to 0.53 ± 0.75 (times/month) during the JTT administration period. In the most effective case, a 13-month-old female, the frequency of AOM decreased from 8.28 times/month to 0 times/month. Duration of fever

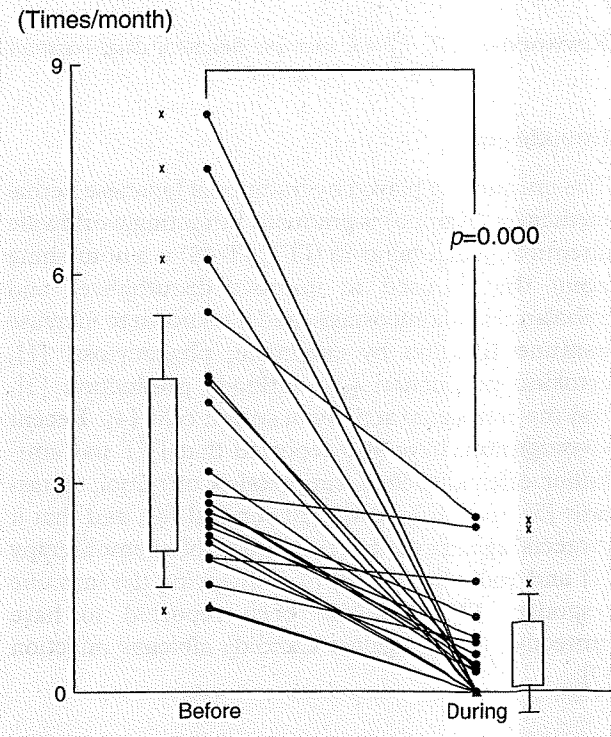

Figure 1. Frequency of AOM before and during JTT administration. Number of occurrences of AOM were counted before and during JTT administration in 21 patients. The average frequency of AOM per month (30 days) was calculated and compared before and during JTT administration. The frequency of AOM decreased significantly with JTT (Wilcoxon signed rank test, $p = 0.000$) (mean $\pm$ SD; before, 3.41 ± 2.00; during, 0.53 ± 0.75).

($p=0.000$) (Figure 2) and antibiotics administration ($p=0.001$) (Figure 3), as well as the number of hospital visits ($p=0.001$) (Figure 4) and emergent hospital visits ($p=0.000$) (Figure 5) decreased significantly during the JTT administration period.

Two of three patients who could not continue taking JTT required the surgical insertion of a ventilation tube due to recurrent otitis media. In addition, 1 of the 21 cases (1 of 42 ears) taking JTT also needed this surgery, as recurrence of otitis media continued, albeit at a lower frequency than before JTT administration. The other 20 patients (95.2%) showed remission and had no need of the surgical insertion of a ventilation tube.

After the end of the JTT administration period, 14 of 21 (66.7%) patients started to take JTT again, as they experienced purulent otitis media and/or other infections after discontinuation of JTT, and their parents decided to resume JTT. Intermission times before resumption of JTT in these 14 patients ranged from 4 to 166 days (mean $\pm$ SD $=41.2\pm$ 51.3 days). Administration periods of JTT after resumption were decided as part of the patients' clinical course. Twelve of 14 children have already finished JTT due to spontaneous recovery from recurrent AOM. We compared the frequency of AOM among the following periods: first administration, during intermission, and after resumption.

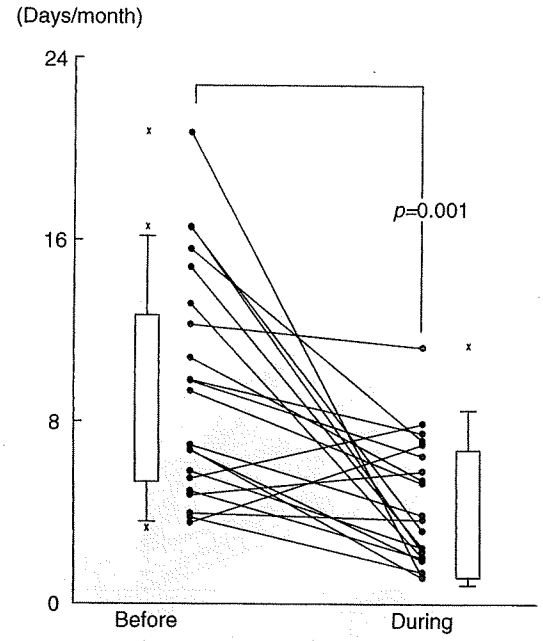

Figure 3. Administration of antibiotics before and during JTT administration. Average number of days of antibiotic administration per month decreased significantly after JTT administration ($p=0.001$) (mean $\pm$ SD; before, 9.62 ± 5.02; during, 4.36 ± 2.77).

With regard to patients taking JTT for more than 3 months after resumption, we investigated the frequency of AOM during the 3 months after restart

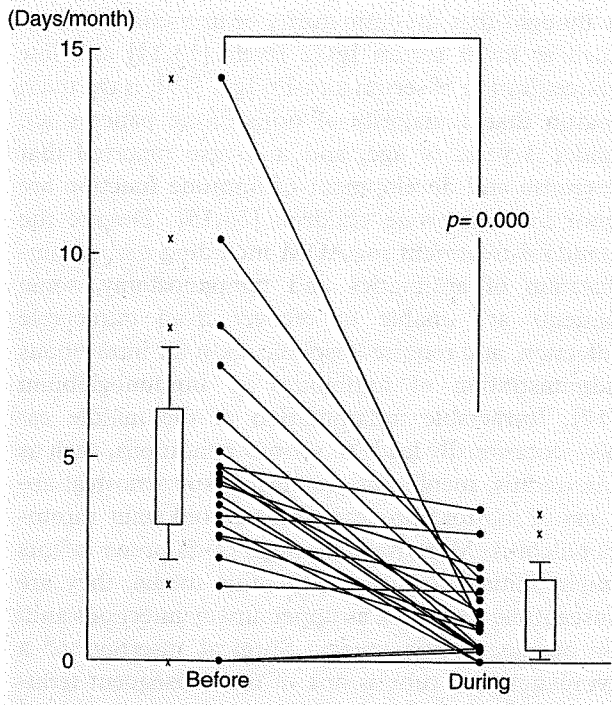

Figure 2. Duration of fever before and during JTT administration. Average duration of fever per month during JTT administration showed a significant decrease vs before JTT administration ($p=0.000$) (mean $\pm$ SD; before, 4.74 ± 3.25; during, 1.15 ± 1.04).

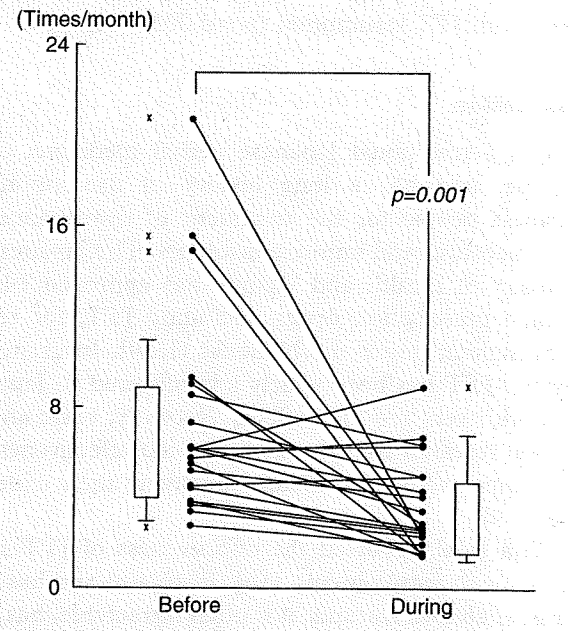

Figure 4. Total hospital visits before and during JTT administration. Total scheduled and unscheduled hospital visits to otolaryngology, pediatrics, and emergency departments for any reasons related to patient condition were counted and calculated as per month (30 days). Significant decreases in number of hospital visits were seen with oral administration of JTT ($p=0.001$) (mean $\pm$ SD; before, 7.28 ± 4.57; during, 3.59 ± 2.05).

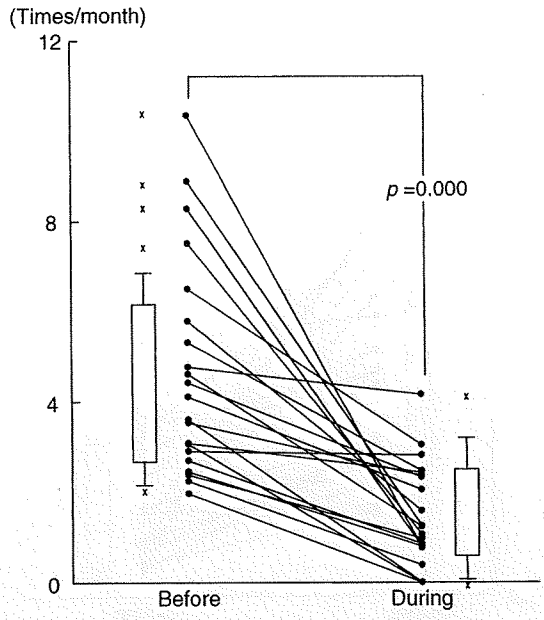

Figure 5. Emergent hospital visits before and during JTT administration. Unscheduled hospital visits due to unexpected circumstances, such as sudden fever, infectious symptoms, and other diseases, were defined as emergent hospital visits. Emergent hospital visits per month decreased significantly with JTT administration ($p=0.000$) (mean$\pm$SD; before, 4.69 ± 2.39; during, 1.49 ± 1.13).

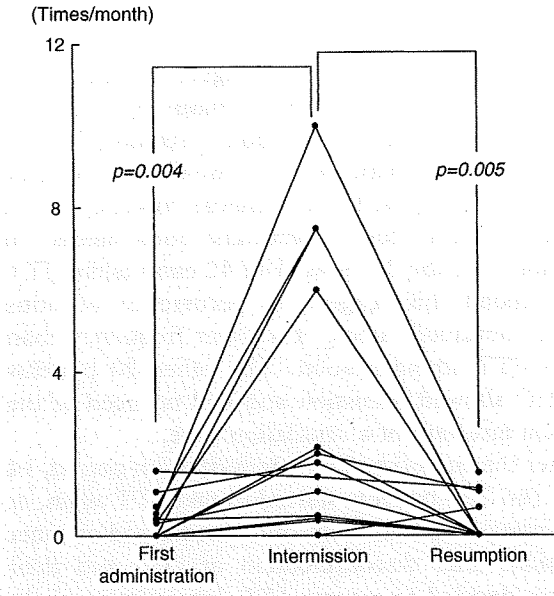

Figure 6. Frequency of AOM in 14 cases resuming JTT; comparison between first administration, during intermission, and resumption. After the 3 month JTT period, 14 of 21 (66.7%) patients resumed JTT administration, as they experienced purulent otitis media and/or other infections after discontinuation. Comparison of the frequency of AOM showed significant increases after stopping JTT ($p=0.004$), followed by decreases after JTT resumption ($p=0.005$) (mean$\pm$SD; first administration, 0.35 ± 0.48; during intermission, 2.90 ± 3.35; resumption, 0.31 ± 0.54).

of JTT. The frequency of AOM was significantly higher after stopping JTT ($p=0.004$) and decreased again with JTT resumption ($p=0.005$) (Figure 6).

Discussion

JTT is a traditional Japanese herbal medicine, or Kampo, and has a long history of use among Japanese people for the treatment of disturbances in homeostasis and immune disorders. The Japanese Ministry of Health and Welfare has approved 148 Kampo prescription drugs, including JTT, for reimbursement under the National Health Insurance system. JTT has been widely administered to Japanese with very few side effects. Recently, basic and clinical research has demonstrated the effectiveness of Kampo medicines, thereby justifying their wider use [1–9].

Ohya et al. reported the effectiveness of JTT in infants with fistula-in-ano [16]. Fistula-in-ano has a range of clinical features; it is often intractable, has a high relapse rate, and it usually disappears spontaneously before about 15 months of age as immune function matures. They reported that administration of JTT accelerates the recovery of fistula-in-ano patients, and reduces the size of peri-anal abscesses, leading to remission in 90.9% patients.

Otitis media is also a unique disease of infancy. It is thought that the immaturity of immune function, such as lower serum IgG2 levels [13,14] and low concentration of serum anti-P6 IgG [15], is the main reason that a majority of otitis-prone patients are under 3 years of age, and it is also reported that response and development of immune function are poor in otitis-prone children [14,15]. Despite the standard treatment for AOM including oral administration of antibiotics and tympanostomy, some patients are unable to recover from intractable infection, and require hospitalization for intravenous administration of antibiotics or immunoglobulin [17]. Intractable inflammation of the middle ear also occasionally leads to serious conditions, such as mastoiditis, meningitis, cerebritis, subperiosteal abscess of mastoid process, and sigmoid sinus thrombophlebitis. Moreover, although otitis-prone infants might initially recover from otitis media, they are susceptible to relapse as upper airway infections and/or purulent otitis media. Surgical insertion of a tympanostomy tube is one of the subsequent treatment options [18], but this procedure is associated with problems, such as the subsequent necessity of tube removal and the possibility of persistent tympanic perforation.

In the present study, we administered JTT to otitis-prone infants in an effort to improve their immune function. The effects of JTT on otitis-prone individuals had not been investigated before. We showed that the frequency of AOM decreased significantly after JTT administration, as compared with before. Significant decreases in the duration of fever and antibiotics administration, and in number of hospital visits and emergent hospital visits were seen with oral administration of JTT. These results suggest that JTT administration to otitis-prone infants also has benefits with regard to medical economics.

Twenty-one of 24 children (87.5%) had no difficulties in taking JTT. No apparent side effects were recognized. Two of three patients who could not take JTT required surgical ventilation tube insertion for recurrent otitis media. Only 1 of the 21 cases (one of 42 ears) taking JTT needed the surgery after recurrence of otitis media, while the other 20 patients (95.2%) showed remission.

Resumption of JTT administration was considered for children who exhibited frequent relapse of otitis media and/or other infections after the first administration period ended. In fact, 14 of 21 (66.7%) patients started to take JTT again. It was also shown that the frequency of AOM increased significantly during the intermission period and again decreased after resumption of JTT.

JTT is thought to be an effective treatment for otitis-prone cases, and avoidance of the overuse of antibiotics will help prevent the emergence of drug-resistant bacteria. With regard to the onset and progression of infection, increased host immune function may be a viable alternative approach for treatment.

This investigation was an open trial and we observed significant therapeutic effects for JTT. However, a randomized, controlled trial is required to further clarify the efficacy of JTT in otitis-prone children.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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急速動注化学療法による上顎洞癌治療

—CDDP投与量との関連について—

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室野重之[1)]　近藤悟[1)]　高仲強[2)]
古川仭[1)]

要　旨

目的：進行上顎洞癌に対する放射線同時併用動注化学療法におけるシスプラチン投与量と治療効果の関連性について統計学的に解析し，本治療法の有効性及びシスプラチン至適投与量を検討すること。

対象と方法：Stage Ⅲ以上の上顎癌22例のうち動注を2コース以上施行した15例についてシスプラチン投与量により2群，すなわちlow-dose群は450mg/body以下（2001年から2003年，n＝7，観察期間5～60ヶ月，中央値26ヶ月）と，high-dose群は600mg/body以上（2004年から2006年，n＝8，観察期間10～32ヶ月，中央値19ヶ月）に群分けし，low-dose群をhistorical controlとしてhigh-dose群の臨床効果，有害事象について検討した。

結果：粗生存率，無増悪生存率ともにhigh-dose群がlow-dose群よりも良好な成績を示したが有意ではなかった。しかし，low-dose群では7例中5例で上顎部分切除術以上の救済手術を必要としたのに対し，high-dose群では部切は1例も施行されなかった（p＝0.0138，x2乗検定）。有害事象は差を認めなかった。

結論：上顎洞癌に対して臓器温存を達成するためには総量600mgのシスプラチン動注が必要である。

キーワード：上顎癌，動注，シスプラチン，化学療法，放射線

Clinical evaluation of efficacy of infused CDDP dose in superselective intra-arterial chemoradiotherapy for maxillary sinus cancer:

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Summary

To evaluate the treatment efficacy of infused dose of cisplatin in intra-arterial chemoradiotherapy for maxillary sinus cancer, patients treated with superselective chemoradiotherapy were divided into a low-dose group (<450mg/body of cisplatin, n＝7, follow-up period 5-60 months, median follow-up 26 months) and a high-dose group (>600mg/body of cisplatin, n＝8, follow-up period 10-32 months, median follow-up 19 months). Of 22 cases, 15 cases who had received at least 2 courses of intra-arterial infusion of cisplatin were involved in this study. The high-dose group had a better overall survival rate and progression-free survival although it was not statistically significant. However, 5 of 7 patients in the low-dose group received partial maxillectomy or more invasive salvage surgery whereas none of the high-dose group did (p＝0.0138). There was no significant difference of adverse effects in the two groups. These results suggest that 450mg of cisplatin is insufficient to control maxillary sinus cancer but 600mg of cisplatin is beneficial.

Key words：Maxillary sinus cancer, Intra-arterial chemotherapy, Cisplatin, Chemotherapy, Radiotherapy

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吉崎　智一

はじめに

1994年Robbinsらは放射線同時併用シスプラチン急速大量動注化学療法を発表した。それは，150mg/m2という大量のシスプラチンを超選択的動注化学療法としてweeklyに4回投与し，その際に全身性副作用を軽減するために中和剤であるチオ硫酸ナトリウムを経静脈的に投与するという方法である。resectable，unresectableもひっくるめた頭頸部進行癌に対して約90％の完全奏効（CR）率を示したため一躍注目を浴びた彼らのプロトコールはRADPLATという呼称で定着した[1,2]。一方で，我々も，この動注法の優れた点に着目したが，彼らが第1相試験で設定したシスプラチンの最大耐用用量と推奨用量は腫瘍容積を考慮したものではなく全身性有害事象に基づくものであった。我々は彼らの設定したプロトコールをいきなり日本人の頭頸部癌，とくに，resectableな症例にも適応可能であるか確信が持てなかった。そこで，1997年当施設で行ったパイロットスタディの結果に基づいて以下のごとく投与量を決定した。すなわち，通常のスケジュールである3週に1回という投与間隔で放射線治療と同時併用で3コースとした。そして，一回投与量は動注したシスプラチンは静注したチオ硫酸ナトリウムで中和されることから，全身性副作用による推奨用量の設定ではなく，気道浮腫などの局所反応を指標に100mg/bodyを標準とし，周囲組織に広く進展し，複数の栄養血管を持つ腫瘍や巨大な腫瘍には150mg/bodyと設定した。そして，世界的に治療方針がcontroversialであるresectableな症例については効果が不十分な場合には外科治療へ方向転換するプロトコールを頭頸部癌治療に応用してきた。その結果，比較的腫瘍容積の小さい下咽頭や喉頭では動注により良好な局所制御が得られたのに対し，腫瘍容積の大きな上顎や口腔進行癌における局所制御は不十分であることが明らかとなった[3-6]。そこで，2003年から上顎洞癌，舌癌などの腫瘍容積の大きなものに対しては150mg/body×4コースを放射線治療と同時併用で施行してきた。

本研究の目的は，進行上顎洞癌に対する放射線同時併用シスプラチン急速大量動注化学療法におけるシスプラチン投与量と治療効果の関連性について統計学的に解析し，本治療法の有効性及びシスプラチン至適投与量を検討することである。

対象と方法

レトロスペクティブスタディ。2001年から2006年まで金沢大学耳鼻咽喉科で診断治療後12ヶ月以上経過したStage Ⅲ以上の上顎洞原発扁平上皮癌22例について治療方法と治療成績の関係について解析を行った。seldinger法によるシスプラチン急速大量投与法を施行した例は17例であった。そのうち2コース以上施行可能であった15例についてシスプラチン投与量により2群，すなわち，450mg/body以下（n＝7，観察期間5～60ヶ月，中央値26ヶ月）のlow-dose群と600mg/body以上（n＝8，観察期間10～32ヶ月，中央値19ヶ月）のhigh-dose群に分類した。実際は2001年から2003年にかけて治療を受けた群がlow-dose群で2004年から2006年がhigh-dose群に相当する。患者内訳は表1に示すとおりで両群に明らかな偏りはなかった。そして，low-dose群をhistorical control群としてhigh-dose群の臨床効果および有害事象について検討した。

動注方法はこれまでの報告と同様である。low-dose群は1回100mgのシスプラチンを2～3回，反応により手術に変更とするプロトコールである（図1）。それに対しhigh-dose群は1回150mgのシスプラチンを4回投与，放射線治療終了4週後腫瘍の遺残が明らかな場合手術というプロトコールを設定した（図2）。経動脈的に投与するシスプラチンの400倍モル比のチオ硫酸ナトリウムを同時に末梢から投与すること，メイロンでpHを調整すること，血管内皮保護のために動注終了時にデカドロン2mgをカテーテルから投与することは両群とも同様である。また，いずれの群も放射線治療66Gy同時併用である。改善点は上顎洞内圧上昇による疼痛を軽減するためhigh-dose群では，上顎洞内に貯留した壊死組織清掃のための小開洞を口嚢部に設置した点である。

統計解析には1）生存解析：生存曲線はKaplan-meier法にて行い，生存率の比較にはLog-Rank法を用いた。

表1　各群の患者内訳

CDDP low（＜450mg）					
	N0	1	2a	2b	計
T3	3			1	4
T4a	1				1
T4b	2				2
計	6			1	7

CDDP high（600mg）					
	N0	1	2a	2b	計
T3	1			1	2
T4a	4			1	5
T4b	1				1
計	6			2	8

UICC 6th edition, 2002

STAGE	
Ⅲ	3例
Ⅳa	2例
Ⅳb	2例

STAGE	
Ⅲ	1例
Ⅳa	6例
Ⅳb	1例

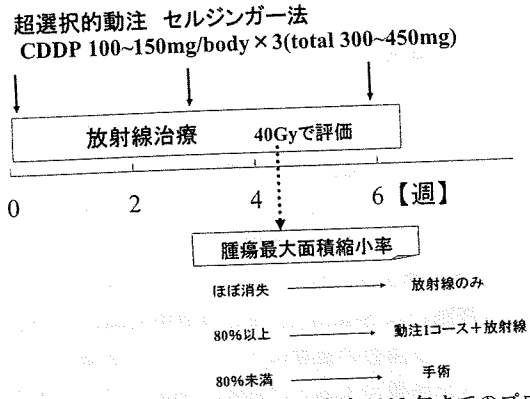

図1　放射線同時併用急速動注化学療法2003年までのプロトコールシェーマ

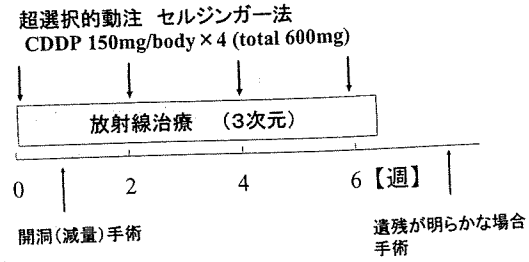

図2　放射線同時併用急速動注化学療法2003年までのプロトコールシェーマ

表2　手術の内訳

	Low-dose 群 n＝7	High-dose 群 n＝8	
上顎部分切除（再建なし）	4	0	P＝.0138
上顎部分切除（再建あり）	1	0	
頸部郭清	0	2	
上顎洞開窓	0	8	

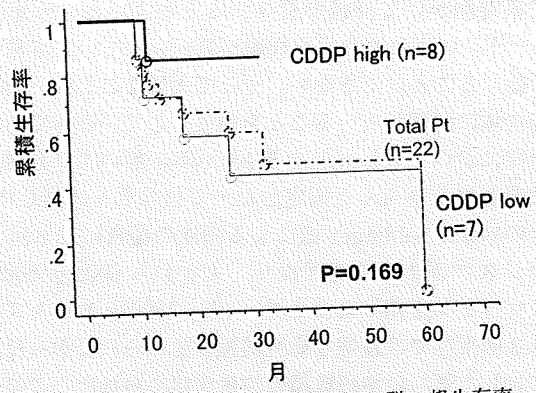

図3　high-dose 群および low-dose 群の粗生存率
CDDP high：high-dose 群，CDDP low：low-dose 群

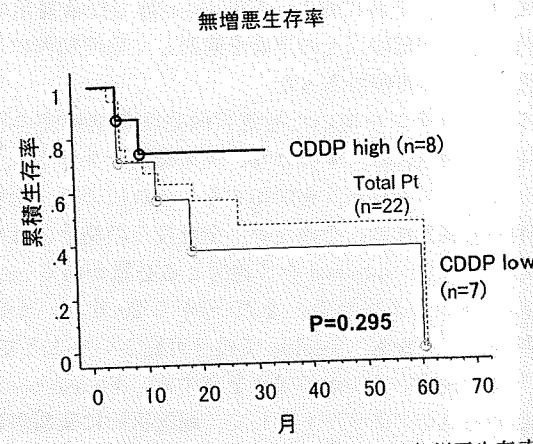

図4　high-dose 群および low-dose 群の無増悪生存率
CDDP high：high-dose 群，CDDP low：low-dose 群

2) low-dose 群と high-dose 群における局所制御および上顎部分切除術の頻度は Fisher の直接法により評価した。$P < 0.05$ を持って統計学的に有意とした。

結　果

患者分布と経過

low-dose 群では7例中5例が効果不十分と判定され照射40Gy，動注2コースの時点で上顎部分切除術をうけた。そのうち2例は原病死，1例は他病死した。残りの2例は動注3コースと66Gyの放射線治療終了後4週の時点でPRと判定された。high-dose 群では8例中6例がCR，2例がPRであった。CRの6例は現在まで無病生存中である。しかし，PRであった2例はいずれも原病死している。low-dose 群のうち1例および high-dose 群のうち2例に初診時リンパ節転移を認めた（表1）。いずれも N2b であった。これらの患者は頸部も照射野に加えられた。頸部郭清術は経過観察中に残存が疑われた high-dose 群の2例に施行された（表2，図3）。

生存率

high-dose 群は観察期間が短いため厳密な比較はできないが，粗生存率，無増悪生存率ともに high-dose 群のほうが良好であった。しかし，統計学的な有意差は得られなかった（図3，4）局所制御については，low-dose 群は4例が，high-dose 群では7例で原発巣制御が可能であった。

局所制御

局所制御率は両治療群間で有意差は認めなかった（P＝0.282）しかし，上記の局所制御を得るために，low-dose群ではhigh-dose群に比べて統計学的に有意に多数の上顎部分切除術以上の手術が施行された（P＝0.0138）（表2）。

有害事象

Grade Ⅲの副作用はlow-dose群，high-dose群ともに1例ずつに認められた。いずれも好中球減少で自然回復した。その他，粘膜炎，赤血球減少，血小板減少，腎機能障害などの有害事象はいずれもGrade Ⅱ以下で，発生率に差を認めなかった。

考　察

腫瘍容積は化学放射線療法の効果に影響をおよぼす重要な因子である[7]。喉頭や下咽頭癌に比べ上顎洞癌は腫瘍体積が大きい。そのため，これらの容積が小さめの癌と同様のシスプラチン投与量では，上顎洞進行癌を化学放射線でコントロールするには十分でない。本研究では限られた対象症例数であるため，局所制御率，無増悪生存率，そして，粗生存率に関して，high-dose群が勝っていたものの統計学的に有意ではなかった。しかし，この差のない生存率を得るために，low-dose群では，有意に多くの症例で術後多少とも顔面の変形を伴う部分切除術以上の手術が必要であった。それに対し，high-dose群では清掃用の小孔を作成したが部切以上の手術を回避して局所制御の目的を果たすことが可能であった。

シスプラチンを用いた超選択的動注化学療法の利点は以下に集約される。すなわち，チオ硫酸ナトリウム全身投与によりシスプラチンを中和する。それにより，全身性副作用が軽減される。そのため，全身投与の場合には数時間かけて投与し，intervalを3週間とる必要があるintensityの高い量のシスプラチンを10分から20分という短時間で投与し，しかも，weeklyで投与可能ということである。一方で動注はいくつかの欠点を有する。disease controlの観点から見たデメリットとして，超選択的に薬剤が到達する領域には高濃度のシスプラチンが到達するが，それ以外の領域ではシスプラチンが中和されることから，転移巣に対する抗腫瘍効果は期待しにくいことがあげられる。一方で，動注により高濃度の薬剤が原発巣へ到達するためリンパ流によって所属リンパ節にも高濃度のシスプラチンが移行して，その結果，頸部リンパ節制御率も上昇するとの報告もある[8]。頸部リンパ節転移は予後不良といわれる上顎洞癌であるが，本検討においてもN2b例は頸部郭清を施行した2例も含め，群を問わず，全例死亡している。したがって，現時点では，腫瘍容積が大きくリンパ節や遠隔転移が少ない上顎洞癌はシスプラチン動注化学療法のよい適応であるがリンパ節転移を有する例ではそれだけでは不十分であり，抗がん剤全身投与との併用などの対策が必要と考えられる。

1970年代Satoらが浅側頭動脈法による上顎癌に対する5-FU動注併用放射線治療成績を報告した後，動注の第一次ブームとなった[9]。他の頭頸部癌に対しては予想されたような効果は発揮できず，この方法は今日の「動注」ほど多施設で施行されなかった。では，現在盛んに行われるようになった「動注」との相違点はどこか。粘膜炎を増強する5-FUに替わり，粘膜障害が軽微であるシスプラチンを大量に使用することに加え，CTアンギオで腫瘍全範囲をカバーするように栄養血管を把握し，その上でシスプラチン投与血管の選択が可能となったことが極めて大切である。動注経路にはSeldinger法と浅側頭動脈法がある。前者のメリットは複数の血管にアプローチできること，後者のメリットは留置できることがあげられる[10]。いずれにしても最も重要な要素は，腫瘍の血行支配の評価法にある。上顎洞癌は顎動脈からの血行支配が優勢であるが，前方は顔面動脈からの血流，上方は前後篩骨動脈すなわち内頸動脈からの血流を受ける。当科では，支配血管のバリエーションに対応可能なSeldinger法を採択している。選択した血管の腫瘍への血流をCTスキャンにより評価したうえでシスプラチンを投与している。手技的には，顎動脈のみの血行支配であれば浅側頭動脈法で十分対応可能と考えられる。しかし，治療経過と共に腫瘍の血行動態は変化してくることを念頭に置いておくべきである。

シスプラチンの用法についても腫瘍を大量のシスプラチンに短時間暴露する，すなわち，最高血中濃度を可能な限り高める方が有効性が高いという意見とAUCを考慮して数時間かけて持続で投与する方がよいという意見がある[11-13]。いずれも良好な成績が報告されていて本稿で優劣を論じることはできない。そこで大切なことは，薬剤が腫瘍全体に到達していることを前提としている点である。本研究においてもlow-dose群high-dose群いずれも腫瘍への栄養血管をきちんと同定した上で投与量を比較している。その結果，Seldinger法による動注の場合には1回150mgのシスプラチンを4回投与，すなわち600mg/bodyのシスプラチンを用いることで，100～150mgのシスプラチンを3回投与では良好な局所制御が認められなかった上顎癌に対して著しい治療成績の改善が認められた。この投与量はRobbinsの150mg/m^{2}よりは少量であるが，彼らとほぼ同等の治療成績である。Hommaらは1回100mg/m^{2}のシスプラチンを4回投与し，我々とほぼ同様の良好な局所制御率を報告している。100mg/m^{2}はほぼ150mg/bodyに匹敵することから，日本人においては，RADPLAT原法のように150mg/m^{2}まで大量のシスプラチンを投与しなくても十分な局所制御を期待できると推察する[11]。そして，有害事象についてはlow-dose群，high-dose群との間に差は認めなかったこと，多施設で施行されたmulti-RADPLAT（RTOG-9615）と比較して，局所性，全身性，いずれの有害事象も軽度であった[12]。これは，チオ硫酸ナトリウムがシスプラチンを中和するとはいっても，すべてのシスプラチンによる有害事象を中和するわけでないことに起因する。とくに局所では高濃度のシスプラチン

に暴露されることから，全身投与の際と異なった副作用が生じる可能性がある。最も懸念されていることはシスプラチンによる組織障害により，長期生存例で骨壊死などの放射線晩発障害の発生頻度が増加する可能性があることである。長期生存以前に初回治療に失敗すれば元も子もないという意見もあるが，必要以上に多量のシスプラチンを投与するのではなく必要十分な量の薬剤使用を心がけるべきである。

結　語

上顎進行癌に対する放射線同時併用シスプラチン急速動注化学療法は，

1) CT アンギオによる腫瘍血行の評価が重要である。

2) 150mg/body×3コース以下のシスプラチンでは局所制御は困難である。

3) 150mg/body×4コースのシスプラチンを用いた場合，Robbins の原法（150mg/m2×4コース）よりも軽度の副作用で，ほぼ同様の局所制御が期待できる。

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JOHNS
特集■口腔癌にどう対応するか―症例から学ぶ

口腔底癌

late T 2・T 3 症例の化学療法・放射線治療

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● Key Words ●口腔底癌，late T 2・T 3，放射線化学療法●

はじめに

近年，頭頸部癌の治療においてもQOLの観点から臓器温存を目指した治療の確立が求められている。口腔底は非常に狭い領域であるため口腔底癌に対する手術治療は大きな機能欠損を残す可能性がある。

本稿では，口腔底扁平上皮癌late T 2・T 3症例に対する化学療法・放射線治療の役割について解説する。

I．過去に報告された口腔底癌の治療成績

これまでの報告によると，口腔底癌全体の5年生存率は60%[1]から65%[2]である。病期別の5年生存率は病期Iで95%から72%，病期IIで86%から63%，病期IIIで82%から44%，病期IVで52%から32%である[2~4]。

一般に口腔底癌に対する治療の第一選択は手術であり，口腔底癌のみの集団で化学療法・放射線治療の成績を報告したものは少ない。一宮らが報告した口腔底扁平上皮癌の放射線治療成績は，病期I＋IIの5年生存率69%，III＋IVの5年生存率51%であった。そして，化学療法を併用した群では全例局所制御されたことから，局所進行口腔底癌に対する化学療法の有効性を示唆している[5]。

他には口腔底癌を含めた頭頸部癌症例におけるneoadjuvant chemotherapyとしての動注化学療法や全身化学療法の有効性に関する報告が散見されるが，確固たるevidenceを得るにいたっていない[6,7]。

II．当科における口腔底癌治療の変遷

当科では，拡大手術の限界が見えた90年代後半から各種頭頸部癌に対して積極的に放射線化学療法の臨床研究を行い，各臓器・各病期に最も適した放射線化学療法のレジメンの確立に努めてきた。現在では交替療法，放射線併用全身化学療法，放射線併用動注化学療法などを原発臓器や病期に応じて選択している[8,9]。

当科が頭頸部進行癌治療にSeldinger法による超選択的動注化学療法を導入した当初はlate T 2・T 3口腔底癌に対しても動注を行った。高い肉眼的CR率を得られたものの局所制御率は低く，ほとんどが再発した(理由は後述)。そのため動注導入後も切除可能症例に対しては手術を優先してきた。

しかし，late T 2およびT 3症例の局所切除には可動部舌や下顎骨の一部を切除しなければならない症例もある。それらの症例は局所欠損が大きく，その修復には遊離組織移植や有茎皮弁による再建が必要となる。そのため術後の構音・咀嚼・嚥下機能の低下は避けられず，QOLの低下を招く結果となった。拡大手術を行っても，当科における口腔癌の治療成績は必ずしも満足のいくものではなかった。

III．当科で行っている口腔底癌の放射線化学療法

当科における口腔底癌late T 2・T 3症例に対する治療は現在も手術が中心である。late T 2・T 3であっても深部への浸潤傾向が少ない腫瘍の場合には，切除後欠損の修復は植皮などで十分可

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