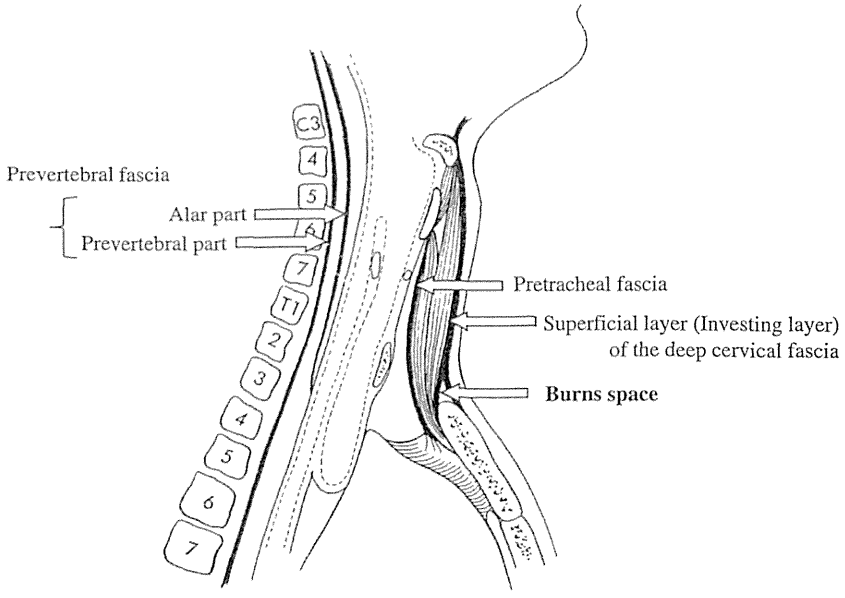
Fig. 1 The suprasternal space [7]



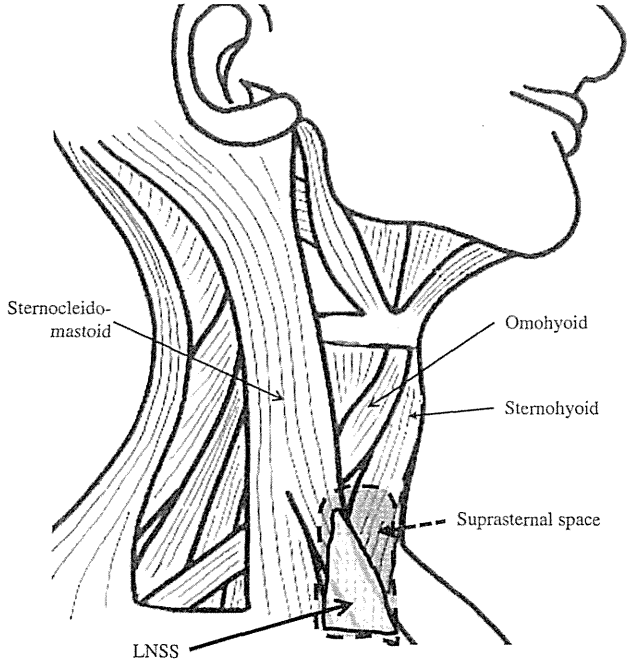


Fig. 2 The suprasternal space and lymph node metastasis between sternocleidomastoid and sternohyoid muscles (LNSS)

aspiration cytology from the level IV lymph node led us to suspect thyroid papillary cancer. She received left hemithyroidectomy and left neck dissection together with dissection of the suprasternal space. Pathological examination revealed papillary cancer in the thyroid without extrathyroidal invasion and multiple lymph node metastases in her left neck (Fig. 4) and suprasternal space. Lymph node metastases were found at level III in her right neck 4 years after the surgery, but she has refused further surgery to date. The follow-up period is currently 11 years and she is

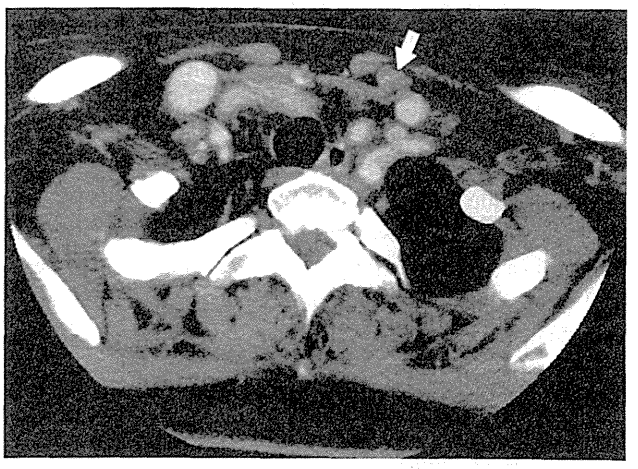


Fig. 3 A lymph node in the left suprasternal space (case 1)

alive and well with lymph node metastasis in the right neck.

Case 2

A 58-year-old male patient visited our department due to lymph nodes in his bilateral neck discovered by ultrasound examination during a medical checkup. He did not complain of any symptoms in his head and neck area. CT scans and ultrasound examination showed tumors in bilateral lobes of the thyroid, lymph nodes in bilateral neck and a lymph node of 0.7 cm in diameter with calcification in the left suprasternal space (T2N1bM0, stage IVA, Fig. 5). The largest lymph node was 1.6 cm in diameter. Fine needle aspiration cytology from the thyroid revealed papillary cancer. He undertook total thyroidectomy, bilateral central

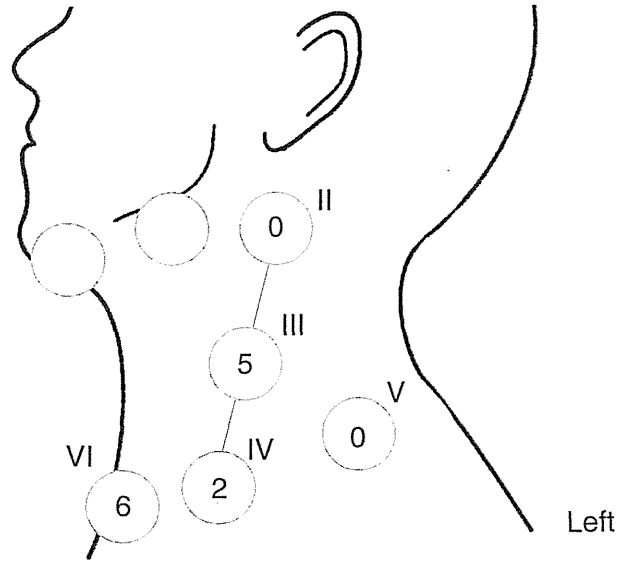


Fig. 4 Number of pathological lymph node metastasis (case 1)

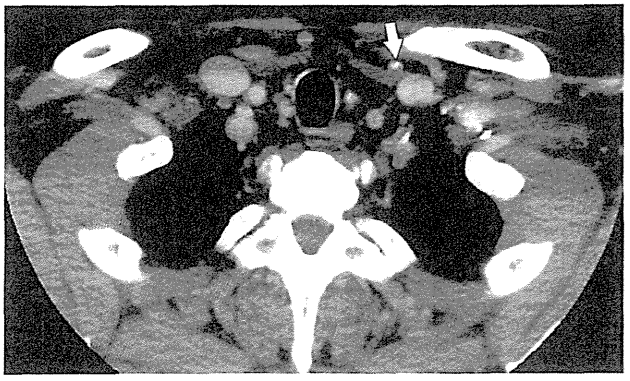


Fig. 5 A lymph node in the left suprasternal space (case 2)

and lateral neck dissection together with dissection of the left suprasternal space. Pathology revealed papillary cancer in the bilateral thyroid with perithyroid soft-tissue extension and multiple lymph node metastases in his bilateral neck (Fig. 6) and suprasternal space. He underwent postoperative radioactive iodine remnant ablation. He is currently alive without disease after follow-up for 2 years.

Discussion

Sun et al. first defined the lymph node between the sternocleidomastoid and sternohyoid muscle (LNSS) as follows (Fig. 2): the anterior boundary is the sternocleidomastoid muscle; posterior boundary, the sternohyoid muscle; superior boundary, the intersection of sternocleidomastoid and sternohyoid muscles; and inferior boundary, the suprasternal fossa and clavicle. Its external and internal boundaries were defined as the lateral and internal borders of the sternohyoid muscle, respectively [2]. They mentioned that the space forms part of the suprasternal space. According to their definition, it is difficult to decide whether fibrofatty tissue anterior to the sternohyoid muscle, above the clavicle and the sternum and medial to sternocleidomastoid muscle belongs to LNSS or not. We consider that what is special about the concept of the LNSS is that it is very close to level VI but divided from it by a strap musculature involving the sternohyoid and sternothyroid muscles, and is not included in level VI. The surgical boundary of the medial border of levels III and IV is the lateral border of the sternohyoid muscle [3]. Therefore, the space anterior to the sternohyoid muscle above the clavicle and the sternum, which could not fall under the normal subdivisions of the central compartment and lateral neck areas, is also included in the concept of the LNSS. Therefore, the anterior boundary of the LNSS should be the anterior layers of the deep cervical fascia above the manubrium of the sternum or the sternocleidomastoid muscle. However, the space anterior to the sternohyoid muscle above the clavicle and the sternum is equivalent to the suprasternal space. Therefore, we propose this space to be called the suprasternal space.

No literature has indicated direct lymphatics from the thyroid and other head and neck cancer to the suprasternal space. However, we supposed that LNSS (hereafter suprasternal space) metastasis is seen once in a while, especially in advanced cases. Sun et al. [2] reported that, without exception, patients with suprasternal space metastasis also had lateral cervical lymph node metastasis. Level III and IV metastases, in particular, were significantly correlated with suprasternal space metastasis. Level VI metastasis, on the other hand, was not correlated with suprasternal space metastasis. Sun et al. speculated that suprasternal space metastasis could be a result of the increasing tumor load after lateral cervical metastasis, or the communication between the superficial or deep anterior cervical chain and the deep lateral cervical chain. We also speculate that fibrofatty tissue including level III and IV metastatic lymph nodes moves into the suprasternal space little by little due to the daily motion of the neck.

In the two cases reported here, lymph node metastasis in the suprasternal space was found by preoperative ultrasound examination and CT scans, and the metastatic node was removed simultaneously with thyroidectomy and neck dissection. However, there is some debate as to whether prophylactic dissection of the suprasternal space should be undertaken or not. We consider that almost all thyroid surgeons do not routinely dissect the suprasternal space. Similarly, we have not dissected the space in any patients apart from the two reported here, yet no patient in our experience has developed lymph node metastasis in the

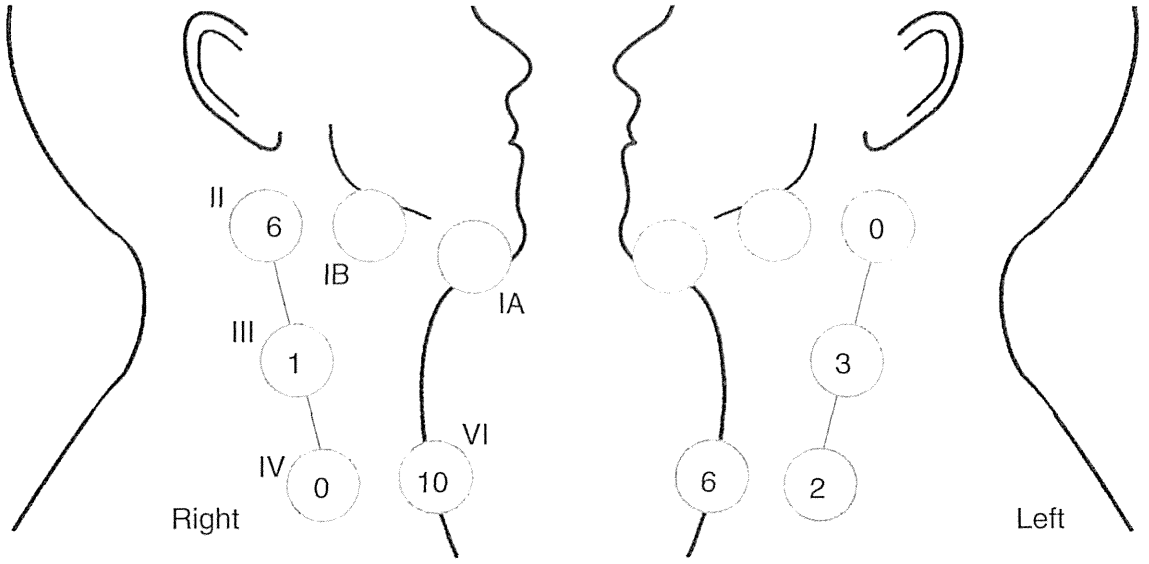


Fig. 6 Number of pathological lymph node metastasis (case 2)

suprasternal space to date and we have not seen any reports of suprasternal space metastasis in cases of thyroid cancer. Sun et al. [2] reported that the positive rate for the suprasternal space was 22.6 % among 115 patients with clinically node-positive thyroid papillary cancer who underwent neck dissection that included the suprasternal space. If dissection is performed, pathological metastasis is suspected to be found in a considerable number of cases. We speculate that the situation is similar to that of central compartment neck dissection. While the frequency of central lymph node metastasis in thyroid carcinoma is high (60–80 %), recurrence rates remain low at 0–15 %, even in patients undergoing total or partial thyroidectomy [4–6]. Therefore, we consider that dissection of the suprasternal space is not necessary as part of routine treatment, but it should be undertaken when preoperative examination suggests suprasternal space metastasis. However, dissection of the suprasternal space is less invasive and easy to achieve and is not time consuming, unlike central compartment dissection, which increases the risk of recurrent laryngeal nerve palsy and hypocalcemia. Therefore, in cases where suprasternal space metastasis is suspected, dissection of the suprasternal space should be performed without hesitation. And we should consider excising the nodal tissue in the suprasternal space in patients with level III and/or IV nodal metastases [2].

In conclusion, there has been no report of the suprasternal space in thyroid cancer to date, and thanks must be given to Sun et al., because of whose paper we became aware of the existence of the suprasternal space in relation to thyroid cancer management. Greater attention should be paid to it as an area with the potential for lymph node metastasis from thyroid cancer.

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Conflict of interest All of the authors declare that they have no conflict of interest.

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Clinical Trial Note

OXFORD

Clinical Trial Note

Dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT-MSC)

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Abstract

A dose-finding and efficacy confirmation trial was started in Japan in April 2014 to evaluate the efficacy and safety of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer. A total of 18 patients will be enrolled in the dose-finding phase for the determination of the recommended number of cisplatin cycles, and 65 patients with T4aN0M0 and 62 patients with T4bN0M0, including those who received the recommended number of or fewer cycles in the dose-finding phase, will be enrolled from 16 institutions within a 5-year period in the efficacy confirmation phase. The primary endpoints of the dose-finding and the efficacy confirmation phases are dose-limiting toxicities and 3-year overall survival, respectively. This trial was registered at the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/) under Trial No. UMIN000013706.

Key words: maxillary sinus cancer, squamous cell carcinoma, chemoradiotherapy, intra-arterial, cisplatin

Introduction

Malignant tumors of the maxillary sinus are rare neoplasms accounting for 0.5% of all malignant diseases, and constituting ~70% of all malignancies of the paranasal sinuses and nasal cavity (1). Most maxillary sinus cancers are at an advanced stage at the time of initial presentation because of the absence of symptoms in early stage disease. Also, only 10–20% of patients with advanced disease develop lymph node metastasis (2). Locally advanced and resectable tumors (cT3N0M0 or cT4aN0M0) require radical surgery with or without a complete resection of the orbital contents as a standard treatment. This often results in significant disfigurement and impairment of function in patients with T4aN0M0 tumors, but this is seldom the case of those with cT3N0M0 tumors. The 3-year overall survival (OS) for 30 patients with cT4aN0M0 who were mainly treated with surgery between 2006 and 2007 at the member institutions of the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group

(JCOG) was reported to be 81.9% (3). This can be regarded as relatively high, but a significant number of patients refuse radical surgery because of disfigurement and functional impairment. Therefore, the development of a new, less invasive therapy that is as effective as radical surgery is critical.

On the other hand, radical surgery is not indicated for unresectable, locally advanced tumors (cT4bN0M0) and concurrent intravenous chemotherapy and radiotherapy (IV-CRT) is regarded as a community standard treatment in daily practice. However, the 3-year OS for seven patients in the JCOG retrospective study was 14.3% (3). This indicates that more effective therapies are necessary for cT4bN0M0.

Chemoradiotherapy (CRT) is one of the promising treatment options for locally advanced laryngeal and pharyngeal squamous cell carcinoma. However, CRT does not necessarily lead to satisfactory treatment outcomes in cases of maxillary sinus cancer (4,5). Recently, superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy (hereafter RADPLAT) has been performed for the patients with locally advanced sinonasal cancer in several institutions and has been reported to result in a favorable survival (6–9). The feasibility and efficacy of RADPLAT were also demonstrated in a multi-institutional setting (10). The intra-arterial infusion procedure for RADPLAT involves the introduction of a transfemoral microcatheter angiographically to the branch of the external carotid artery supplying the tumor. Cisplatin is then infused through the microcatheter to the dominant blood supply of the targeted tumor. At the same time, sodium thiosulfate is infused systemically to neutralize the cisplatin.

This procedure is now used in Japan with 100 mg/m^2 generally administered per cycle, although the number of the cycles of cisplatin infusion varies (4–7 cycles) by institution. On the other hand, in the original report by Robbins et al., (11,12) 150 mg/m^2 was administered once a week for only four cycles. Theoretically, repeating cisplatin infusion while patients receive radiotherapy is more effective as it increases the radiosensitization efficacy of cisplatin. However, the number of cycles of cisplatin at a dosage of 100 mg/m^2 has not been optimized, and we have incorporated a dose-finding phase in this study to determine the recommended number of cisplatin cycles.

Against this background, we have undertaken a dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer (JCOG1212, RADPLAT–MSC). The recommended number of cisplatin cycles in the dose-finding phase is to be determined by a study of patients with both T4aN0M0 and T4bN0M0 tumors. The analyses in the efficacy confirmation phase will be conducted separately for patients with T4aN0M0 and for those with T4bN0M0. Patients with lymph node metastasis were excluded to ensure homogeneity of the population and evaluate the efficacy of RADPLAT more clearly as they were reported to have a poorer prognosis than those without lymph node metastasis (6,13).

The Protocol Review Committee of the JCOG approved the protocol in February 2014 and the study was activated in April 2014. This trial was registered at the UMIN Clinical Trials Registry under Trial No. UMIN000013706 (http://www.umin.ac.jp/ctr/).

Purpose

Dose-finding phase

The objective of the dose-finding phase is to evaluate the incidence of dose-limiting toxicity (DLT) and determine the recommended cycle of intra-arterial infusion of cisplatin in combination with concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

Efficacy confirmation phase

The objective of the efficacy confirmation phase is to confirm the efficacy and the safety of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

Study design

A multi-institutional open-label, dose-finding and non-randomized confirmatory trial.

Endpoints

Dose-finding phase

The primary endpoint of the dose-finding phase is the incidence of DLT. The secondary endpoint is the incidence of adverse events.

Efficacy confirmation phase

The primary endpoint of the efficacy confirmation phase is 3-year OS in all eligible patients including those who received the recommended number of or fewer cycles in the dose-finding phase. The secondary endpoints are OS, event-free survival, local event-free survival, clinical complete remission rate, the incidence of adverse events and the incidence of serious adverse events.

OS is defined as days from enrollment to death from any cause, and it is censored at the latest day the patient is alive. Event-free survival is defined as days from enrollment to either the first event of any disease progression such as primary disease, lymph node metastasis or distant metastasis, salvage surgery or death from any cause. Local event-free survival is defined as days from enrollment to either the first event of primary disease progression, salvage surgery or death from any cause. Event-free survival and local event-free survival are censored at the latest day the patient is alive without any evidence of adverse events. Clinical complete remission rate is the proportion of patients with a complete response or good partial response (good PR) among all eligible patients. A good PR is defined as a residual secondary change with tumor shrinkage, such as when the residual tissue is regarded as scar material rather than a residual tumor. Our evaluative guidelines suggested that defining good PR lesions as those 10 mm or less in size and not enhanced on contrast-computed tomography scans.

Eligibility criteria

Inclusion criteria

For inclusion in the study, the patient must fulfill all of the following criteria:

(i) Primary lesion located at the maxillary sinus
(ii) Histologically proven squamous cell carcinoma
(iii) Clinical stage T4aN0M0 or T4bN0M0
(iv) No severe carotid stenosis as evaluated by ultrasonography
(v) Age between 20 and 75 years (dose-finding phase) or between 20 and 80 years (efficacy confirmation phase),
(vi) ECOG performance status of 0 or 1
(vii) No prior therapy for maxillary sinus cancer
(viii) No prior radiation therapy to the head and neck or the brain
(ix) No prior chemotherapy for any other malignancies

(x) Sufficient organ function
(xi) Normal electrocardiogram
(xii) Suitability for angiography
(xiii) Satisfying normal tissue radiation dose constraints for the ipsilateral eyeball and optic nerve, spinal cord, brainstem and chiasma
(xiv) Written informed consent.

Exclusion criteria

Patients are excluded if they meet any of the following criteria:

(i) Simultaneous or metachronous (within 5 years) double cancers, except *in situ* carcinoma or intramucosal tumor
(ii) Active infection requiring systemic therapy
(iii) Body temperature ≥38°C
(iv) Women during pregnancy, during breastfeeding or within 28 days after delivery
(v) Severe psychosis
(vi) Need for systemic steroid medication or immunosuppressant medication
(vii) Poorly controlled diabetes mellitus
(viii) Poorly controlled hypertension
(ix) Angina pectoris attack within 3 weeks or myocardial infarction within 6 months
(x) Positive for serum HBs antigen

Quality control of intra-arterial chemotherapy

Fifteen institutions among the Head and Neck Cancer Study Group of the JCOG are initially participating in this trial. All participating interventional radiologists have agreed to the technical details for superselective intra-arterial chemotherapy pre-specified in the study protocol. To control the quality of the interventional technique, central review of photographs and movies in arbitrarily selected patients will be performed at a semiannual investigators' meeting. All interventional procedures are performed or directly supervised by interventional radiologists certified by the study chair. The major criteria for certification in this study include either (i) having experienced interventional radiology on ≥40 occasions with ≥10 occasions as the principal operator, (ii) having experience with two patients or more requiring intervention with superselective arterial infusion of cisplatin for head and neck cancer within 2 years or (iii) being board certified in societies related to interventional radiology.

Treatment methods

Chemotherapy

The protocol treatment consists of weekly intra-arterial infusion of cisplatin with concomitant radiotherapy and salvage surgery if necessary. In the dose-finding phase, 100 mg/m^2 of cisplatin is administered intra-arterially weekly for 7 weeks. At the same time, sodium thiosulfate is administered at a dose of 20 g/m^2 intravenously to neutralize the cisplatin. The recommended number of cycles of cisplatin will be determined in the dose-finding phase and applied in the efficacy confirmation phase.

Radiation therapy

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 70 Gy in 2 Gy fractions five times weekly. The gross tumor volume (GTV) includes the volume of the primary tumor. The clinical target volume (CTV) includes the GTV with a 0.5 cm margin and at least the entire ipsilateral maxillary sinus. The CTV does not include potential lymph node metastasis area in the neck. The planning target volume (PTV) for the CTV is defined as a 0.5 cm margin around the CTV to compensate for set-up variations and internal organ motion. To protect normal vital structures, such as the contralateral eye ball and/or optic nerve, chiasma, spinal cord and brain, a partial reduction in the PTV margin of 0.1 cm from the initial 0.5 cm is allowed.

Dose-finding method

In the dose-finding phase, 100 mg/m^2 of cisplatin is administered weekly for 7 weeks with concomitant radiotherapy to 18 patients. Cisplatin is skipped in the case of adverse events that meet the skipping rule defined by the protocol. The recommended number of cycles will be determined according to the distribution of the number of cycles of administered cisplatin and the incidence of DLT.

Definition of DLT

The DLT observation period is defined as the period from the date of initiation of CRT to 28 days after the last radiotherapy session. The grade of toxicity will be assessed according to the Common Terminology Criteria for Adverse Events v 4.0. DLT will be defined using the following criteria:

(i) Grade 3 febrile neutropenia
(ii) Grade 4 thrombocytopenia
(iii) Estimated creatinine clearance <40 l/min
(iv) Grade 3 non-hematologic toxicity, except for mucositis, dermatitis, electrolyte abnormalities and complications related to intervention
(v) Radiation break of >14 days due to toxicity
(vi) Skipping chemotherapy administration for 3 or more cycles consecutively
(vii) Treatment-related death.

Follow-up

All enrolled patients are followed up for at least 5 years, while analysis of the primary endpoint of the efficacy confirmation phase is conducted 3 years after accrual completion. Efficacy and safety are to be evaluated at least every 3 months during the first year, at least every 4 months during the second year and then every 6 months during the third to fifth year.

Study design and statistical analysis

This trial is a dose-finding and efficacy confirmation trial to evaluate the incidence of DLT and to determine the recommended number of cycles of intra-arterial infusion of cisplatin in combination with concomitant radiotherapy for patients with locally advanced maxillary sinus cancer in the dose-finding phase. In the efficacy confirmation phase, the objective is to evaluate the efficacy and the safety of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

We set a planned sample size for each cohort to confirm the efficacy of RADPLAT. The sample size in the efficacy confirmation

phase is 65 patients with T4aN0M0 and 62 patients with T4bN0M0, including the eligible patients in the dose-finding phase but not the patients who received more than recommended number of cycles of chemotherapy in the dose-finding phase with 3 years of follow-up and an accrual period of 5 years.

In the T4aN0M0 patients, the 3-year OS was 81.9% in the observational study undertaken on our group. Thus, the sample size was set at 65 patients, which provided 80% power under the hypothesis of primary endpoint with an expected value of 80% and threshold value of 65% using one-sided testing at a 5% significance level.

In T4bN0M0, the 3-year OS was 14.3% in the observational study undertaken on our group. Thus, the sample size was set at 62 patients, which provided 80% power under the hypothesis of primary endpoint with an expected value of 35% and threshold value of 20% using one-sided testing at a 5% significance level. To test the hypothesis, we used the 3-year OS estimated by the Kaplan–Meier method and its confidence interval based on Greenwood's formula.

Interim analysis and monitoring

No interim analysis is planned. If the number of cases with treatment-related death and severe (Grade 2 or more) cerebrovascular ischemia reaches six and seven, respectively, registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves continuation of the trial. The JCOG Data Center is responsible for data management, central monitoring and statistical analysis. JCOG Data Center also provides semiannual monitoring reports, submitted to and reviewed by the JCOG Data and Safety Monitoring Committee. None of the physicians performing the interventions will be involved in the data analysis. For quality assurance, site-visit audits, not for a specific study basis but for the study group basis, will be performed by the JCOG Audit Committee.

Participating institutions (from North to South)

Hokkaido University Hospital, Iwate Medical University, Tohoku University Hospital, Miyagi Cancer Center, Saitama Cancer center, National Cancer Center Hospital East, National Hospital Organization Tokyo Medical Center, Tokyo University Hospital, Japanese Foundation for Cancer Research, Cancer Institute Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kinki University hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University Hospital, Hyogo Cancer Center and Nara Medical University.

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Conflict of interest statement

None declared.

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頭頸部癌　40(4)：490-496，2014

当院における再発・転移頭頸部がんに対するドセタキセル・シスプラチン併用（DC）療法の遡及的解析

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森本浩一[4] 斉藤　幹[4] 西村英輝[3]
大月直樹[4] 佐々木良平[3] 丹生健一[4]

要　旨

目的：再発・転移頭頸部がんに対するドセタキセル・シスプラチン（DC）療法の安全性および効果について後方視的に検討する。

対象および方法：2006年7月から2012年10月までにDC療法を実施した再発・転移頭頸部がん患者24例。

結果：扁平上皮癌（上咽頭がん3例を除く）17例を対象とする有効性に関する検討では，奏効割合47%（完全奏効 18%，部分奏効 29%），生存期間中央値390日，無増悪生存期間中央値188日であった。全24例を対象とする安全性に関する検討では，有害事象は発熱性好中球減少が8例（33%）にみられ，そのうち5例は1コース目で発症していた。有害事象のために減量が必要となった，または治療を中止した症例はそれぞれ12例（50%），2例（8%）であった。治療関連死亡は認めなかった。

結論：再発・転移頭頸部扁平上皮癌に対するDC療法は既報と同程度の治療効果を示した。実施にあたっては発熱性好中球減少に対する適切な対応が必要と考えられた。

キーワード：ドセタキセル，シスプラチン，緩和的化学療法，発熱性好中球減少

Safety profile and efficacy of Chemotherapy with Docetaxel and Cisplatin (DC) for Recurrent or Metastatic Head and Neck Cancer-A Retrospective Analysis in a Single Institution:

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Summary

Purpose: To assess the safety profile and efficacy of chemotherapy with docetaxel plus cisplatin (DC) for recurrent or metastatic head and neck cancer, we retrospectively reviewed the medical chart of the patients in our institution.

Patients and methods: From July 2008 to October 2012, twenty-four patients with recurrent or metastatic head and neck cancer were treated with chemotherapy with DC. DC was administered until disease progression or unacceptable toxicities. DC consisted of docetaxel (DTX) 60～70 mg/m^2 d1 and cisplatin (CDDP) 75～80 mg/m^2 d1.

Results: We identified 17 patients with recurrent or metastatic squamous cell carcinoma of head and neck excluding 3 patients with nasopharyngeal carcinoma. We included these 17 patients in efficacy analysis. DC achieved response rate of 47 % (complete response 18 %, partial response 29 %) and median overall survival and progression free survival were 390 days and 188 days, respectively. All of the 24 patients were included in safety analysis. Following grade 3/4 adverse events, including neutropenia (79%), anemia (17%), febrile neu-

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tropenia (FN, 33%), nausea (4%), anorexia (21%), stomatitis (4%) and diarrhea (17%) were observed. Of the eight patients complicated with FN, five patients suffered from FN at first course of DC. Twelve patients (50%) needed dose reduction of DC due to toxicities and 2 patients (8%) had to discontinue DC due to unacceptable toxicities. No treatment related death was observed.

Conclusion: Considering that this study was small sample sized retrospective analysis, chemotherapy with DC appeared to have at least similar efficacy to those reported previously. Because of the high incidence of FN, we have to take care of prevention and management of FN.

Key words：Docetaxel, Cisplatin, Palliative chemotherapy, Febrile neutropenia

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はじめに

これまで，再発・転移頭頸部扁平上皮癌（Recurrent or Metastatic Squamous Cell Carcinoma of Head and Neck, R/M-SCCHN）に対する全身化学療法は，過去の臨床試験の結果からシスプラチン（CDDP）を含む2剤併用療法が標準的であると認識されてきた。そのような中で，Vermorken らは R/M-SCCHN 患者を対象に，5-フルオロウラシル（5-FU）と CDDP を併用する FP 療法に上皮成長因子受容体（Epidermal Growth Factor Receptor, EGFR）に対する抗体薬であるセツキシマブ（Cetuximab, C-MAb）を上乗せする効果を検証する第Ⅲ相ランダム化比較試験を行い，FP + C-MAb 療法が全生存期間（Overall Survival, OS）および無増悪生存期間（Progression Free Survival, PFS）において FP 療法を上回ることを示した（EXTREME study）[1]。この結果と国内第Ⅱ相試験の結果[2]から我が国においても C-MAb は 2012 年 12 月に頭頸部がんに対して適応追加され，海外における R/M-SCCHN に対する標準治療である FP + C-MAb 療法が，日本においても使用可能となった。

タキサン系抗がん薬であるドセタキセル（DTX）を CDDP と併用する DC 療法は 2000 年代前半に複数の第Ⅱ相試験で安全性，有効性が検討され[3-7]，FP 療法と並んで R/M-SCCHN に対する緩和的化学療法の選択肢の一つと考えられている[8]。しかし，日本人の R/M-SCCHN 患者に対する DC 療法の安全性及び有効性に関する報告は少ない。

当科では DC 療法を再発・転移頭頸部がんに対する緩和的化学療法として実施してきたため，その安全性及び有効性を検討したので報告する。

対象および方法

2006 年 7 月より 2012 年 10 月までに当院で DC 療法による全身化学療法を行った頭頸部がん患者 24 例について後方視的に検討した。

DC 療法は以下の 2 種類の方法で投与した。A：DTX 60 mg/m^2，CDDP 80 mg/m^2，day1，3 週間毎，B：DTX 70 mg/m^2，CDDP 75 mg/m^2，day1，3 週間毎。

A が 20 例，B が 4 例に対して行われていた。

各抗がん薬の減量は以下のように行った。DTX は，発熱性好中球減少を発症した場合または DTX に起因する Grade3 以上の非血液毒性出現時に次コースより DTX を 20％減量した。CDDP は糸球体濾過量（Glomerular Filtration Rate, GFR）が 50 ml/min 以上 60 ml/min 未満で 20％減量し，40 ml/min 以上 50 ml/min 未満では 40％減量した。また CDDP に起因する Grade 3 以上の非血液毒性（電解質異常を除く）出現時に次コースより CDDP を 20％減量した。ただし，聴力障害は Grade 2 以上で 20％減量した。

2～3 ヶ月毎に頭頸部内視鏡，CT/MRI などを用いた画像診断による効果判定を行い，病勢進行もしくは耐容できない毒性が出現するまで，4 ～ 6 コースを目標に治療を継続した。支持療法として，十分な補液を 3 日間程度行い，悪心・嘔吐予防として 5-HT3 受容体拮抗薬（グラニセトロンまたはパロノセトロン），デキサメタゾン，NK-1 受容体拮抗薬（アプレピタントまたはフォスアプレピタント）を使用した。

有害事象，治療コンプライアンスについては全例（n = 24）を検討対象とした。有害事象は CTCAE ver.4.0 を用いて評価し，血液毒性（好中球数，ヘモグロビン値，血小板数），非血液毒性（発熱性好中球減少，悪心・嘔吐，食欲不振，粘膜炎，肝障害，腎障害）について全 Grade および Grade3/4 の頻度を算出した。治療コンプライアンスについては実施コース数，Relative Dose Intensity（RDI），減量または中止した症例数およびその理由を検討した。

本治療法の効果については，非扁平上皮がんおよび上咽頭がんを除いた R/M-SCCHN（n＝17）を対象に検討した。腫瘍縮小効果は，RECIST ver 1.1 に基づいて評価した。生存期間については，2013 年 7 月末日をカットオフ日とした全生存期間（Overall Survival, OS），無増悪生存期間（Progression Free Survival, PFS）を Kaplan Meier 法を用いて推定した。OS，PFS の定義はそれぞれ治療開始日から死亡日（すべての死因による），治療開始日から腫瘍の増悪もしくは死亡（すべての死因による）のいずれかの早い方までとした。

結 果

1. 患者背景

対象患者の背景をTable1.に示す。88％が男性で年齢の中央値は64歳であった。組織型は83％が扁平上皮癌であった。扁平上皮癌症例の原発部位は下咽頭が最も多く，以下口腔，中咽頭，上咽頭，喉頭，鼻副鼻腔が続いた。非扁平上皮癌の4症例は大唾液腺または外耳道原発であった。67％が既治療例で，診断時点で遠隔転移を伴う未治療例は33％ であった。初発例8例の担がん部位は，原発巣8例，リンパ節8例，遠隔転移6例，再発例16例の担がん部位は，原発巣6例，リンパ節9例，遠隔転移11例であった（重複あり）。再発例16例中，先行治療として手術が15例，放射線治療（化学放射線療法を含む）は16例に行われていた。化学療法は11例に行われ，そのうち10例がプラチナ系抗がん薬を含む化学療法であった。先行するプラチナ系抗がん薬の最終投与日から腫瘍増悪までの期間（Platinum-Free Interval，PFI）が6ヶ月未満の症例は11例中1例であった。

2. 安全性および治療コンプライアンス

24例に対し，91コースが行われた。実施コース数別の症例数は，3コース以下10例(42％)，4コース6例(25％)，5コース以上8例（33％）で，実施コース数の中央値は4コース（範囲1～6コース）であった。11例において治療中止となっており，中止理由の内訳は病勢進行7例，合併症2例（重複癌の悪化，口腔皮膚婁各1例），有害事象2例であった。有害事象により中止となった2例の詳細は，せん妄を伴った発熱性好中球減少（Febrile Neutropenia，FN）が1例，ドセタキセルに対するGrade 3のInfusion reactionが1例であった。

薬剤の減量は24例中12例（50％），91コース中28コース（31％）で行われ，RDIはDTX 90％（範囲58～100％），CDDP 84％（51～100％）であった。減量の理由および症例数・減量されたコース数（重複あり）は血清クレアチニン(Cre)上昇5例・11コース，FN 4例・10コース，食欲不振2例・5コース，下痢 1例・2コース，Radiation recallに伴う粘膜炎1例・2コース，テタニーを伴う低Mg血症1例・2コースであった。

有害事象（Table2）は好中球減少（Grade 3以上79％）の頻度が高く，非血液毒性（Grade 3以上）はFN（33％），食欲不振（21％），下痢（17％），口内炎（4％）などを認めた。FNを発症した8例中5例は1コース目で発症しており，2コース目，3コース目，5コース目で発症した症例が各1例であった。FNを発症した8例は，全例治療開始時のPSが1であり，PS0の7例でFNを発症した症例はなかった。また，治療関連死亡は認めなかった。

3. 治療効果

R/M-SCCHNにおける腫瘍縮小効果は完全奏効（Complete Remission，CR）3例（18％），部分奏効（Partial Remission，PR）5例（29％），不変（Stable Disease，SD）6

Table 1 Patient Characteristics

	Number of patients（％）
Gender	
Male	21（88％）
Female	3（12％）
Age	
Median	64
Range	36～73
Histology	
Squamous Cell Carcinoma	20（83％）
Adenoid Cystic Carcinoma	1（ 4％）
Acinic cell Carcinoma	1（ 4％）
Mucoepidermoid Carcinoma	1（ 4％）
Unclassified	1（ 4％）
Primary site	
Sinonasal	1（ 4％）
Oral Cavity	5（21％）
Nasopharynx	3（13％）
Oropharynx	4（17％）
Hypopharynx	6（25％）
Larynx	1（ 4％）
Salivary gland	3（13％）
Others	1（ 4％）
Timing of Diagnosis	
Newly diagnosed	8（33％）
Recurrent	16（67％）
Metastasis	
M0	7（29％）
M1	17（71％）
Prior Treatment	
Surgery	15（63％）
Definitive	10（42％）
Salvage	5（21％）
Radiotherapy/CRT	17（71％）
Definitive/Preoperative	7（29％）
Adjuvant	7（29％）
Palliative	3（13％）
Chemotherapy	11（46％）
Platinum-based	10（42％）
PFI＜6 months	1（ 4％）
PFI≧6 months	9（38％）
Others	4（17％）
Complicated malignancy	
Synchronous	5（21％）
Metachronous	3（13％）

PFI：Platinum Free Interval，m：Month

Table 2　Adverse events（AEs）

	All grades（%）	Grade 3-4（%）
Hematological AEs		
Neutropenia	96	79
Anemia	92	17
Thrombocytopenia	13	0
Non-hematological AEs		
Nausea	88	4
Anorexia	88	21
Diarrhea	38	17
Constipation	33	0
Peripheral neuropathy	25	0
Creatinin increase	21	0
Stomatitis	17	4
Infusion reaction	8	0
Febrile neutropenia	33	33

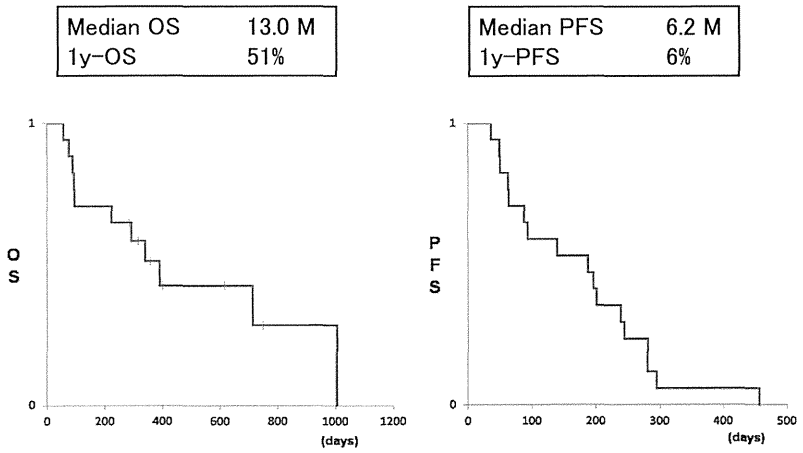

Fig. 1　Survival of RM-SCCHN treated with DC
OS：Overall Survival, PFS：Progression-Free Survival,
R/M SCCHN：Recurrent or Metastatic Squamous Cell Carcinoma of Head and Neck, M：months, y：year

例(35%)，病勢進行(Progressive Disease, PD) 3例(18%)であり，奏効割合（Overall Response Rate, ORR）47%，病勢コントロール割合（Disease Control Rate, DCR）82%であった。

OSおよびPFSをFig.1に示す。生存例の観察期間中央値は386日（範囲 286～751日）であった。OSの中央値は390日，1年生存割合は51%であった。PFSの中央値は188日，1年無増悪生存割合は6%であった。

上咽頭癌を除く頭頸部扁平上皮癌（n＝17）に対する治療効果を初発例（n＝6）および再発例（n＝11）について解析・比較すると，ORRは83%および27%，1年生存割合は63%および45%，1年無増悪生存割合は17%および0%であった。

考　察

DC療法はシスプラチン併用化学療法の一つであり，R/M-SCCHNに対する緩和的化学療法の選択肢の一つとして用いられてきた。海外で実施された第Ⅱ相試験における用量はDTX 75～100 mg/m^2，CDDP 70～75 mg/m^{2}であり（Table3）[3-7]，DTX 75 mg/m^2, CDDP 75 mg/m^{2}が代

Table 3 Previous reports of chemotherapy with DC for SCCHN

Author	Design	Patients	Dose and number of cycles	Incidence of FN	ORR (CR rate)	mOS
Schoffski[3] (1999)	Phase Ⅱ Single-arm Multi-center	LA/R/M (n = 44)	DTX 100 mg/m^2 d1 CDDP 75 mg/m^2 d1 4 cycles (Median)	6%	54% (15%)	1 year-OS 50%
Specht[4] (2000)	Phase Ⅱ Single-arm Multi-center	R/M (n = 25)	DTX 75 mg/m^2 d1 CDDP 75 mg/m^2 d1 5 cycles (Median)	8%	33% (8%)	11m
Baur[5] (2002)	Phase Ⅱ Single-arm Single-institutional	LA/R/M (n = 30)	DTX 80 mg/m^2 d1 CDDP 70 mg/m^2 d1 6 cycles (Median)	13%	53% (20%)	Not reported
Gedlicka[6] (2002)	Phase Ⅱ Single-arm Single-institutional	R/M (n = 40)	DTX 75 mg/m^2 d1 CDDP 75 mg/m^2 d1 6 cycles (Maximum)	Infection ≧ Grade 3 13%	53% (18%)	11m
Glisson[7] (2002)	Phase Ⅱ Single-arm Multi-center	LA/R/M (n = 36)	DTX 75 mg/m^2 d1 CDDP 75 mg/m^2 d1 4 cycles (Median)	6%	40% (6%)	9.6m

DC：Docetaxel + Cisplatin SCCHN：Squamous cell carcinoma of head and neck
FN：Febrile neutropenia ORR：Overall response rate mOS：Median overall survival
LA：Locally advanced R：Recurrent M：Metastatic DTX：Docetaxel CDDP：Cisplatin
CR：Complete response m：Months

表的なレジメンとされている[8]。今回の検討対象において行われたAレジメンは，進行非小細胞肺がんに対するレジメンとして，Bレジメンは非小細胞肺がんや再発・転移頭頸部がんに対する化学療法として報告されていたものである。日本でドセタキセルの頭頸部がんに対する保険承認用量上限が60 mg/m^2，70 mg/m^2，75 mg/m^{2}と変更されたのに伴い，当科で行われたDC療法もAレジメンからBレジメンに移行し，現在はDTX 75 mg/m^2，CDDP 75 mg/m^{2}を用いている。本研究は前向き研究でないため2つのレジメンにおいて目標コース数，実施コース数にばらつきがあり，また症例数も両者の相違を十分検出できる数に達していないことから，2群間で治療効果，有害事象の比較を行う意義は乏しいと考えられ，両群を合わせて各アウトカムの検討を行った。

DC療法はDTXを使用するため血液毒性が比較的強く出ると考えられ，本検討においてもやはり血液毒性が顕著であった。海外で行われたDC療法の第Ⅱ相試験におけるFNの頻度は6～13%と報告されているが[3-7]，本検討におけるFNの頻度は33%と高かった。このため，DC療法を行なう際には何らかのFNに対する予防策が必要である。具体的にはG-CSF予防投与と抗菌薬予防投与が考えられる。ASCOガイドライン[9]やEORTCガイドライン[10]でもFNが20%以上の頻度で起こると予測される化学療法におけるG-CSFの一次予防投与を推奨している。本検討でもFNを発症した8例中5例が1コース目で発症し，FN発症頻度33%という点を考慮すると，G-CSFの一次予防投与が有益である可能性が考えられる。しかし，いずれのガイドラインでもG-CSF予防投与は根治的化学療法を受ける患者において推奨されており，本検討の様な治癒不能な再発・転移患者に対しては推奨されず，我々もFNを発症した患者において次コース以降抗がん薬を減量することでFNの再発を回避する方針としていた。また，IDSAのガイドラインでは好中球数＜500/μlが7日間以上持続する場合に抗菌薬予防投与が推奨されており[11]，推奨される抗菌薬としてシプロフロキサシンまたはレボフロキサシンが挙げられている。抗菌薬予防投与は耐性菌の増加につながるため，低リスク症例へ一律に行う事は避けられるべきだが，耐性獲得率をモニタリングしながら高リスク症例を対象に抗菌薬予防投与を行うことは許容されるかもしれない[11]。さらに，FNの予防策として，抗がん薬の開始用量を減らすという対応も考慮すべきである。しかし，この用量設定は頭頸部がん[3-7]および非小細胞肺がん[12-14]において日本人患者を含む臨床試験において安全性が確認された用量であり，今回の遡及的な検討結果のみで開始用量を減量することには注意が必要である。実際に本検討において16例（67%）の患者はFNを理由とした減量を行っておらず，91コース中63コース（69%）は減量せずに実施できていた。さらにFNのために減量されたコース数は10コースと全体の11%にすぎずPS0の症例はFNを発症していなかった。従って，治療効果を維持しつつ安全にDC療法を行うには，PS良好な患者を選択すること，患者の状態に応じて抗菌薬予防投与も考慮すること，FNを発症した場合には適切に減量を行うことで対応するのが妥当と考えられる。

Table 4　Previous reports of palliative chemotherapy for R/M SCCHN

Author (year)	Design	Number of patients	Regimen	ORR	mPFS	mOS
Vermorken[1] (2008)	Phase Ⅲ	220	FP or FC	20%	3.3 m	7.4 m
	Randomized-Controlled	222	FP or FC + C-MAb	36%	5.6 m	10.1 m
Gibson[17] (2005)	Phase Ⅲ	104	CDDP + 5-FU	29.8%	Not reported	8.7 m
	Randomized-Controlled	100	CDDP + PTX	26.0%		8.1 m
Urba[19] (2012)	Phase Ⅲ	397	CDDP + Placebo	8%	2.8 m	6.3 m
	Randomized-Controlled	398	CDDP + PEM	12%	3.6 m	7.3 m
Kiyota[18] (2009)	Retrospective	43	FP	30%	3.0 m	9.8 m
Current Study	Retrospective	17	CDDP + DTX	47%	6.2 m	13.0 m

ORR：Overall response rate，mPFS：Median progression free survival，mOS：Median overall survival，
CDDP：Cisplatin，DTX：Docetaxel，C-MAb：Cetuximab，PEM：Pemetrexed　PTX：Paclitaxel
FP：5-FU + CDDP　FC：5-FU + Carboplatin　m：months

FP 療法における下痢の頻度は，欧米で行われた前向き試験で 2.8 ～ 6%[15-17]，日本人患者を対象とした後方視的解析では 3.3% と報告されている[18]。DC 療法は 5-FU を使用しないため粘膜毒性が比較的軽いと考えられたが，本検討では Grade 3 以上の口内炎の頻度は 4% であったが，下痢は 17% と比較的高頻度であった。DC 療法の実施にあたっては DTX の消化管毒性にも十分な注意が必要と考えられた。

R/M-SCCHN に対する緩和的化学療法の標準レジメンは FP + C-MAb 療法であるが，入院下での 5-FU 96 時間連続投与や毎週の C-MAb 投与を必要とするため，患者に入院期間延長や通院回数の増加という負担が生じるという問題点もある。その点で DC 療法は 1 日で抗がん剤の投与が終了するため，毒性のマネージメントが十分できていれば比較的短期間で退院可能で，通院回数も最小限で済むところが有利である。社会的事情から長期入院や頻回の通院が困難で FP + C-MAb 療法の適応が困難な症例，粘膜・消化管毒性を回避したい症例に対して DC 療法は選択肢の一つになると考えられる。

DC 療法の治療効果は，R/M-SCCHN に対する第Ⅱ相試験で ORR 33～54%，OS 中央値 9.6～11 ヶ月と報告されており[3-7]，その他のプラチナ系抗がん薬を含む緩和的化学療法については同様の患者を対象に ORR 12～36%，OS 中央値 7.3 ～ 10.1 ヶ月と報告されている（Table4）[1, 17-19]。これに対して本検討においては ORR 47%，OS 中央値 13 ヶ月という治療成績であった。少数例の後方視的解析であることを考慮しても，DC 療法は過去の報告と少なくとも同程度の効果を持つ治療法であると考えられた。

結　論

DC 療法は R/M SCCHN に対する緩和的化学療法として有望な治療選択肢の一つと考えられた。ただし，治療関連死亡は認めなかったものの，血液毒性が強く発熱性好中球減少の頻度も高いため，本治療法を施行する際には患者の全身状態を考慮して必要に応じて抗菌薬予防投与も検討するなどの工夫が必要と考えられた。

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Review Article

Review Article

Adjuvant treatment for post-operative head and neck squamous cell carcinoma

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Abstract

One of the mainstays of treatment for locally advanced head and neck squamous cell carcinoma is surgery. However, for post-operative patients with high-risk factors for recurrence, surgery alone is insufficient and improving survival requires adjuvant treatment after surgery. Unlike with most other malignancies, the standard adjuvant treatment for post-operative head and neck cancer patients with high-risk factors for recurrence is radiotherapy concurrent with chemotherapy. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative head and neck squamous cell carcinoma.

Key words: head and neck cancer, high-risk factors for recurrence, adjuvant treatment, chemoradiotherapy

Introduction

According to cancer statistics in Japan, 8120 Japanese died from head and neck cancer in 2012, accounting for 2.2% of cancer deaths (1). About half of head and neck cancer patients have Stage III/IV at diagnosis disease and the prognosis of these patients remains poor. Previously, surgery was one of the mainstays of treatment for resectable locally advanced head and neck squamous cell carcinoma (HNSCC), while post-operative radiotherapy (RT) was standard treatment in patients with high-risk factors for recurrence in pathological specimens (2). However, local relapse and distant metastasis relapse rates after post-operative RT were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). To improve the prognosis of post-operative HNSCC with high-risk features, the addition of cisplatin to RT was developed, and showed a survival benefit over RT alone. Now chemoradiotherapy (CRT) with cisplatin (CDDP) at a dose of 100 mg/m^2 is the standard of care for post-operative HNSCC with high-risk factors for recurrence. This review article focuses on the history and future perspectives of adjuvant treatment for post-operative HNSCC.

Adjuvant treatment for post-operative HNSCC

Which patients should receive adjuvant treatment?

The prognosis for Stage III/IV resectable locally advanced HNSCC is poor. Known risk factors for recurrence are: microscopic resection margin-positive, extracapsular nodal extension-positive, multiple cervical lymph node metastasis (≥2), lymph node metastasis with a diameter of 3 cm or more, perineural invasion, Level 4 (inferior internal jugular lymph node) or Level 5 (accessory nerve lymph node) lymph node metastasis in oropharyngeal cancer/oral cavity cancer and signs of vascular tumor embolism. For patients with none of these risk factors, 5-year local relapse rate is only 10%, and post-operative adjuvant treatment is therefore not usually performed. For patients with risk factors for recurrence, post-operative RT has been used as a post-operative adjuvant treatment. However, patients positive for extracapsular nodal extension or those with two or more risk factors for recurrence were reported to have a 5-year local relapse rate of 32% and 5-year survival rate of 42%, showing poor prognosis even after post-operative radiotherapy (4,5). Surgery with post-operative RT is therefore considered insufficient, and more effective treatment has been sought (6).

It is therefore necessary to identify the most important risk factors for recurrence in patients receiving post-operative radiotherapy. A combined analysis was conducted using data from the RTOG 85-03 study (randomized study to compare post-operative radiation with chemotherapy with 5FU + CDDP followed by post-operative radiotherapy in post-operative patients with locally advanced hypopharynx squamous cell carcinoma) and RTOG 88-24 study (Phase II study of post-operative chemoradiotherapy with CDDP in patients after surgery of locally advanced head and neck squamous cell carcinoma) conducted by the Radiation Therapy Oncology Group (RTOG) (6). Results showed that patients with risk factors for recurrence including (i) microscopically positive resection margin, (ii) extracapsular nodal extension-positive and (iii) multiple lymph node metastases (≥2) had a higher 5-year local relapse rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 61 vs. 27 vs. 17%) and decreased 5-year survival rate (microscopically positive resection margin vs. extracapsular nodal extension/multiple cervical lymph node metastasis vs. no relapse risk factor: 27 vs. 34 vs. 53%) compared with patients with none of the above factors. On this basis, improving prognosis in patients with any of these three risk factors for recurrence is particularly important.

In addition to (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, the European Organization for Research and Treatment of Cancer (EORTC) also suggests that Stage III/IV disease, perineural infiltration, Level 4/5 lymph node metastasis in oropharyngeal cancer/oral cavity cancer, and signs of vascular tumor embolism are also risk factors for recurrence (7–10). Despite some differences in the definition of post-operative risk factors for recurrence between the EORTC and RTOG, the two key trials (Table 1), namely the EORTC22931 study (7) and RTOG95-01 study (11), were conducted, as described later. To account for these differing definitions, data from the two studies were consolidated in a combined analysis (8). This indicated not only that CRT with CDDP was generally superior to RT alone as post-operative adjuvant treatment, with the difference between them being significant [hazard ratio (HR), 0.776], but also that post-operative CRT with CDDP is more advantageous than RT alone for patients with either of the common high-risk factors for recurrence observed in the two studies, namely (i) microscopic resection margin positivity or (ii) extracapsular nodal extension positivity (HR = 0.702). In contrast, post-operative CRT with CDDP showed no advantage over RT alone in patients with risk factors for recurrence that were not common between the two studies (e.g. multiple lymph node metastases) in either the EORTC22931 study or the RTOG95-01 study.

Therefore, major high-risk factors for recurrence are presently defined as (i) microscopic resection margin positivity and (ii) extracapsular nodal extension positivity, and patients with either of these major risk factors should receive post-operative CRT with CDDP. Other risk factors for recurrence which were not common between the two studies, including multiple cervical lymph node metastases, are termed intermediate risk factors. The provision of post-operative RT to patients with these intermediate risk factors is based on the results of this combined analysis.

Table 1. Differences in risk factors for recurrence between RTOG and EORTC

Risk factor only in RTOG	Common risk factors with RTOG and EORTC	Risk factors only in EORTC
Multiple lymph node metastases (≥2)	Microscopic resection margin positivity, extracapsular nodal extension positivity	Stage III/IV disease, perineural infiltration, level 4/5 lymph node metastasis in oropharyngeal cancer/ oral cavity cancer, vascular tumor embolism

What is the optimal adjuvant treatment for post-operative high-risk HNSCC patients?

Radiotherapy

Prognosis of Stage III/IV resectable locally advanced head and neck squamous cell carcinoma is poor, and post-operative RT after radical resection has remained the standard treatment for this type of cancer since 1970, when Fletcher et al. (2) published a report on prognosis after post-operative radiotherapy. In conventional post-operative radiotherapy for resectable locally advanced head and neck squamous cell carcinoma, a total dose of 60–66 Gy is commonly used and administered once daily, five times per week at 2.0 Gy as conventional fractionated irradiation with no interval period (7,11). However, local relapse and distant metastasis relapse rates after post-operative radiotherapy were as high as 30 and 25%, respectively, and 5-year survival rate was as low as 40% (3). Thus, post-operative RT is now indicated for patients with intermediate risk factor for recurrence and those at high risk for recurrence who are unsuitable for post-operative CRT due to poor organ function (renal impairment etc.).

Chemoradiotherapy

As described above, post-operative CRT has been developed for the treatment of locally advanced HNSCC in patients at high risk of recurrence. Pivotal randomized trials of post-operative CRT for HNSCC patients at high risk of recurrence are listed in Table 2.

Bachaud et al. reported the results of a randomized comparative study in 83 HNSCC patients with high post-operative risk (extracapsular nodal extension-positive). The RT-alone group had a 5-year overall survival (OS) of 13% whereas that in the CRT (CDDP 50 mg/body every week) group was 36% ($P < 0.01$), showing the statistically significant superiority of post-operative CRT (12).

Smid et al. compared RT alone with CRT using mitomycin (MMC) and bleomycin (BLM) in 114 HNSCC patients with high post-operative risk (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). Although this was a small randomized study, 2-year OS was 64% in the RT-alone group versus 74% in the CRT group, showing that post-operative CRT was significantly superior ($P = 0.036$) (13).

The EORTC22931 study registered 334 patients with any of the risk factors for recurrence of microscopic resection margin positivity, extracapsular nodal extension positivity, Stage III/IV disease, perineural invasion, Level 4 or Level 5 lymph node metastasis (in oropharyngeal/oral cavity cancer), and signs of vascular tumor embolism. Five-year disease-free survival (DFS) was 36% in the RT alone vs. 47% ($P = 0.04$) in the CRT with CDDP groups, and 5-year OS was 40% vs. 53% ($P = 0.02$), showing the superiority of post-operative CRT (7).

The RTOG95-01 study registered 416 patients with any of the post-operative risk factors for recurrence (microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥2). The 2-year local control rate (LCR), the primary endpoint, in the RT alone and CRT groups was 72 vs.

Table 2. Pivotal randomized trials of post-operative chemoradiotherapy

Author		Disease status	*N*	Chemo	RT total, Fr size	LRR	DFS	OS
Bachaud (1996)	5-year data (2-year data)	High risk	39	W-CDDP	65–74 Gy,	23%	45% (68%)	36% (72%)
			44	None	1.7–2 Gy/Fr	41%	23% (44%)	13% (46%)
						$P = 0.08$	$P < 0.02$	$P < 0.01$
Smid (2003)	2-year data	High risk	59	MMC,BLM	56–70 Gy,	14%	76%	74%
			55	None	2 Gy/Fr	31%	60%	64%
						$P = 0.037$	NS	$P = 0.036$
Bernier (2004)	5-year data	High risk	167	3W-CDDP	66 Gy,	18%	47%	53%
			167	None	2 Gy/Fr	31%	36%	40%
						$P = 0.007$	$P = 0.04$	$P = 0.02$
Cooper (2004)	3-year data	High risk	206	3W-CDDP	60–66 Gy,	18%	47%	56%
			210	None	2 Gy/Fr	28%	36%	47%
						$P = 0.01$	$P = 0.04$	$P = 0.19$
Fietkau (2006)	5-year data	High risk	226	5FU,CDDP	50–64 Gy	11%	62%	58%
			214	None	2 Gy/Fr	28%	50%	49%
						$P = 0.0006$	$P = 0.023$	NS
Argiris (2008)	5-year data	High risk	36	CBDCA	59.4 Gy	22%	49%	51%
			36	None	1.8 Gy/Fr	28%	53%	44%
						NS	NS	NS

Chemo, chemotherapy; LRR, local relapse rate; DFS, disease-free survival; OS, overall survival; NS, not significant; Gy, gray; Fr, fraction.

82% ($P = 0.003$) (Gray's test), respectively, showing the superiority of post-operative CRT. In addition, the 3-year progression-free survival (PFS) rate was 36 vs. 47% ($P = 0.04$), again showing the superiority of post-operative CRT. However, 3-year OS was 47 vs. 56%, showing only a trend for the superiority of post-operative CRT, without statistical significance ($P = 0.19$) (11).

At the American Society of Clinical Oncology (ASCO) meeting of 2006, Fietkau et al. (14) presented the results of ARO 96-3, a Phase III study, which compared two post-operative adjuvant treatments: RT alone and CRT with 5-FU + CDDP. This study targeted 440 HNSCC patients with high post-operative risk [microscopic resection margin positivity, extracapsular nodal extension positivity or multiple cervical lymph node metastases (≥3)]. Five-year DFS in the RT alone and CRT groups was 50 vs. 62%, respectively ($P = 0.023$), showing the statistically significant superiority of post-operative CRT, whereas 5-year OS was 49 vs. 58%, respectively, showing no significant difference.

In 2008, Argiris et al. (15) reported the results of a Phase III study on post-operative adjuvant treatment which compared RT alone and CRT with carboplatin in 72 HNSCC patients with high-risk factors (microscopic resection margin positivity, extracapsular nodal extension positivity, perineural invasion or signs of vascular infiltration). In this study, the CRT group showed no superiority to the RT-alone group in either 5-year DFS or 5-year OS, and thus the usefulness of post-operative CRT with carboplatin was not demonstrated.

Regarding the toxicities, acute/late toxicities and statistical comparisons were not consistently reported. Cooper et al. (11) reported that severe acute toxicities in RTOG95-01 study were significantly higher in CRT than RT alone (77 vs. 34%, $P < 0.001$). Moreover, Bachaud et al. (12) also reported that severe acute toxicities tended to be higher in CRT than RT alone (41 vs. 16%) (16). But, in terms of severe late toxicities, there were no significant differences between CRT and RT alone (RTOG95-01; 21 vs. 17%, EORTC22931; 38 vs. 49%) (7,11,16).

Based on the above results and combined analysis of RTOG95-01 study and EORTC22931 study (8), post-operative CRT has been the standard post-operative adjuvant treatment for HNSCC patients at high risk of recurrence (microscopic resection margin positivity or extracapsular nodal extension positivity). CDDP 100 mg/m^2 every 3 weeks, which was used in both the EORTC22931 and RTOG95-01 studies, is believed to be the most common standard regimen for concurrent monotherapy. Regarding the feasibility of post-operative CRT with CDDP at a dose of 100 mg/m^2 in Japanese patients, a Phase II feasibility study (17) reported that 80% (20/25) of patients completed per-protocol treatment. In addition, the safety profile of the study was almost the same as that of the previous studies (7,11) of post-operative CRT with CDDP at a dose of 100 mg/m^2. Thus, post-operative CRT with CDDP at a dose of 100 mg/m^2 is feasible and is the standard of care for Japanese HNSCC patients with high post-operative risk.

Chemotherapy

The role of adjuvant chemotherapy remains to be determined. Concurrent administration of chemotherapy with RT has been investigated since the 1970s, and a few randomized studies of adjuvant chemotherapy for post-operative HNSCC (18–21) have appeared. However, all of these randomized studies comparing treatment for post-operative HNSCC with or without adjuvant chemotherapy failed to show efficacy in this setting. Reports on post-operative adjuvant chemotherapy are also limited in Japan, with only a single study by Tsukuda et al. (22) in 1994, which reported that post-operative adjuvant chemotherapy with UFT significantly decreased distant relapse rate but did not contribute to survival prolongation. Thus, adjuvant chemotherapy is not indicated for post-operative HNSCC patients.

When should post-operative RT or CRT be started?

Appropriate timing to start post-operative RT or CRT is important because theoretically, excessive time from surgical resection will allow the repopulation of microscopic residual tumors, and the efficacy of adjuvant treatment will accordingly decrease. Ang et al. randomized post-operative high-risk HNSCC patients to a total dose of 63 Gy delivered over 5 or 7 weeks. In the 7-week schedule, a prolonged interval between surgery and post-operative RT was associated with significantly lower local control and survival. Overall treatment time from surgery to completion of post-operative RT had a major influence on the 5-year locoregional control rate: for an overall time of <11

weeks, locoregional control was achieved in 76%, compared with 62% for 11–13 weeks and 38% for >13 weeks ($P = 0.002$) (5). This result indicated that post-operative RT should preferably start within 6 weeks after surgery.

Future perspectives for adjuvant treatment for post-operative HNSCC

Adjuvant CRT with CDDP is the current standard treatment for high-risk post-operative HNSCC patients. Despite this treatment strategy, 5-year overall survival in this setting is still ~50% (7,11). Moreover, only 60% of patients in pivotal Phase III trials (7,11) received three cycles of CDDP at a dose of 100 mg/m^2. These findings indicate the need for more efficacious and less toxic adjuvant CRT.

Regarding investigations for more efficacious adjuvant CRT, Harrington et al. reported the final results of a randomized Phase III trial of adjuvant CRT with or without lapatinib for post-operative high-risk HNSCC patients. Lapatinib is a tyrosine kinase inhibitor with targets both EGFR and HER2. Primary endpoint of this study was DFS. Results showed no significant difference in DFS between arms (HR 1.10, 95% CI: 0.85–1.43) and no significant difference between arms in OS, the secondary endpoint (HR 0.96, 95% CI: 0.73–1.25). Taking this result together with that of the RTOG0522 trial, which compared CRT with or without cetuximab in locally advanced HNSCC and also failed to show a survival benefit for cetuximab, the addition of a molecular targeting agent to CRT provides no superiority over CRT. Other approaches may be necessary.

One of the concerns of adjuvant CRT with CDDP at dose of 100 mg/m^2 is insufficient compliance with CDDP delivery, and the use of CRT with weekly CDDP in adjuvant settings has been poorly investigated (12,23,24). CRT with weekly CDDP at 40 mg/m^2 has already shown a survival benefit for nasopharyngeal cancer (25). CRT with weekly CDDP at this dose appears to be safer and more feasible than CRT with CDDP at 100 mg/m^2. However, a small randomized trial (26) showed significantly higher rates of radiation mucositis and overall toxicities for CRT with CDDP at 40 mg/m^2. To clarify these discrepant findings for the safety and efficacy of 3-weekly and weekly schedules, we are now conducting a Phase II/III trial of post-operative chemoradiotherapy comparing 3-weekly with weekly cisplatin in high-risk patients with squamous cell carcinoma of the head and neck, the JCOG1008 study (UMIN Clinical Trial Registry number: 000009125) (27).

Conclusions

Standard adjuvant treatment for post-operative high-risk HNSCC patients is CRT with 3-weekly CDDP at dose of 100 mg/m^2. However, both compliance and treatment outcomes with this schedule are unsatisfactory, and further investigation for more efficacious and feasible adjuvant CRT is warranted.

Conflict of interest statement

None declared.

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JOHNS 特集○大きく変わりつつある頭頸部癌化学療法

海外の臨床試験からみた頭頸部癌化学療法

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● Key Words ●頭頸部癌，化学療法，臨床試験，シスプラチン，分子標的薬●

はじめに

頭頸部癌に対する薬物療法はシスプラチン（CDDP）登場以来，集学的治療の中で大きな役割を持つようになってきている。海外では進行癌に対する生存期間の延長を目指した多くの臨床試験によって薬物療法に関するさまざまなエビデンスが得られている。アメリカではそれらの根拠になるデータを集約してNCCNガイドラインが公表されている。

化学療法における標準治療の端緒となるデータはKishらのCDDPと5-FUの併用療法（FP）の効果に関する報告で，未治療例に対しFPの奏効率が88.5％とする優れた報告を発表している[1]。それ以来，FPは頭頸部癌に対する標準的レジメンと考えられるようになった。その後，化学放射線療法，術後化学放射線療法，そして導入化学療法に関する臨床試験が続き，海外では多くのエビデンスが確立している。

今回，現在の頭頸部癌化学療法の基盤となる海外での臨床試験について述べる。

化学放射線療法のエビデンス

頭頸部癌に対する集学的治療で最もエビデンスが高いのは，化学放射線療法（CRT）である。海外ではCRTに関する多くのランダム化比較試験が行われている。大規模なメタアナリシスが，2000年にPignonらによって報告されている。65のランダム化比較試験で10,850例の症例を対象としたものであり，放射線療法に対して化学療法の同時併用は放射線療法単独と比較して5年生存率で8％の上乗せ効果を認めている[2]。さらに，2009年にはデータが更新され，進行頭頸部癌に対するCRTは標準治療として認識されている[3]。これ以降の第Ⅲ相比較試験でもさまざまな薬剤による併用療法が検討されている。これらの比較試験の大部分は切除不能例を対象としており，ほとんどが放射線治療単独と比較して化学療法併用療法の優位を報告している。

化学放射線療法のレジメン

海外ではCDDPを併用したCRTの多くの臨床試験が行われメタアナリシスによってCDDP併用が標準的レジメンと考えられるようになった[3]。Al-Sarrafらは上咽頭癌に対する多施設共同研究の長期成績を報告しCDDP併用化学放射線療法とFPによる補助化学療法は上咽頭癌の標準的治療となっている[4]。CDDPの投与量は100 mg/m^{2}が世界標準とされ，海外の多くの臨床試験で採用されている。多剤併用療法によるCRTもさまざまなレジメンで施行されているが，その中でも標準的な多剤併用療法であるFP療法を放射線療法と併用するCRTは，海外においても実際の臨床では多くの施設で行われている。

フランスのGORTECからの報告ではStageⅢ・Ⅳの中咽頭癌でカルボプラチンと5-FU併用療法によるCRTにおいて放射線治療単独と比較して5年生存率は31％から51％へ有意に上昇した。しかし重篤な粘膜炎も化学療法の併用療法により39％から71％と高率となっている[5]。最近では，イタリアの臨床試験でHN07試験が行われているが，ここでは放射線療法と併用するレジメンはFP療法である。このようにCRTにおける併用レジメンはCDDP単独が標準とされているにも

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