Intra-arterial chemoradiotherapy for head and neck cancer

Akihiro Homma¹,*, Rikiya Onimaru², Kazuto Matsuura³, K. Thomas Robbins⁴, and Masato Fujii⁵

¹Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, ²Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, ³Division of Head and Neck Surgery, Miyagi Cancer Center, Sendai, Japan, ⁴Division of Otolaryngology-Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, IL, USA, and ⁵Department of Otolaryngology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan

*For reprints and all correspondence: Akihiro Homma, Department of Otolaryngology-Head & Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: ak-homma@med.hokudai.ac.jp

Received 9 July 2015; Accepted 29 August 2015

Abstract

Intra-arterial chemotherapy has been used to treat localized malignant neoplasms in patients with head and neck cancer for over 50 years as the head and neck region is particularly well suited to regional chemotherapy. Early intra-arterial chemotherapy did not prove its efficacy. In addition, the additional complications associated with establishing and maintaining arterial access have further dampened enthusiasm for this approach. Subsequent significant advances in vascular radiology techniques and the development of new devices, such as fluoroscopy units and angiographic catheters, have made possible safe, accurate and repeated superselective intra-arterial chemotherapy. Intra-arterial infusion of high-dose cisplatin with systemic neutralization by intravenous sodium thiosulfate (RADPLAT) is a theoretically attractive approach to the treatment of advanced head and neck cancer. However, a Dutch trial comparing intra-arterial and intravenous chemoradiotherapy for advanced head and neck cancer showed that RADPLAT was not superior to intravenous chemoradiotherapy. Therefore, further investigation of RADPLAT, including the refinement of the indications for its application, is needed.

Key words: intra-arterial, chemoradiotherapy, head and neck cancer, maxillary sinus cancer

Introduction

Head and neck malignancies represent a group of epidermoid tumours that arise from the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses. Approximately 700 000 new cases of head and neck cancer are estimated to occur each year, which accounts for ∼4.9% of new cancer cases in the world (1). Alcohol and tobacco abuse are common aetiologic factors in cancers of the oral cavity, oropharynx, hypopharynx and larynx. In addition, Epstein–Barr virus infection is correlated with the development of nasopharyngeal cancer, and human papilloma virus (HPV) infection is also correlated with the development of oropharyngeal cancer. The incidence of HPV-related oropharyngeal cancer has sharply increased in Japan as well as in Western countries in recent years.

Stage I or II disease defines a relatively small primary tumour with no nodal involvement (2). Affected patients undergo either surgery or radiation therapy with curative intent. This goal is achieved in >80% of patients with Stage I disease and >60% of patients with Stage II disease (3). Stage III and IV cancers include large primary tumours, which may invade underlying structures and/or spread to regional nodes. Distant metastases are uncommon at presentation (2).

Patients with Stage III or IV have traditionally received treatment regimens that include partial and complete removal of organs such as
the larynx, pharynx, tongue and maxilla. Although the disease may be brought under control, substantial impairment of function and appearance related to the therapy remains (4). As a result, it lessens the quality of the patients’ lives and the prognosis for patients with advanced stage disease is much worse than that for patients with early stage disease. Therefore, attempts to treat advanced disease with the aim of improving survival rates without sacrificing function have led to the addition of chemotherapy to the more traditional treatment methods of surgery and radiation therapy. In recent years, chemoradiotherapy, which is the combination of radiation therapy with chemotherapy, has become a viable alternative to surgery for advanced cases.

Intra-arterial (IA) chemotherapy has been used to treat localized malignant neoplasms in patients with head and neck cancer for over 50 years as the head and neck region is particularly well suited to regional chemotherapy. The blood supply to these tumours is primarily derived from branches of the external carotid artery. The natural history of head and neck cancer is to recur at the primary site or in regional neck nodes, while distant dissemination occurs late and is a less frequent cause of morbidity and death (5). Tumour eradication with preservation of function and appearance form the basis of therapy for head and neck tumours. Therefore, the use of IA chemotherapy has been a focus of attention in relation to head and neck cancer for some time.

**Dawn of IA chemotherapy for head and neck cancer**

Klopp et al. (6) were the first to use IA chemotherapy in 1950. They developed a suitable technique for repeated IA injection of nitrogen mustard through polyethylene tubing introduced through a proximal arterial branch directly into the artery. They administered nitrogen mustard to several head and neck cancer patients and reported effects not obtained by the intravenous (i.v.) administration of therapeutic amounts of the same drug. However, the practical usefulness of this form of therapy was severely limited by nitrogen mustard’s lack of specificity and by the severe destructive effects on normal adjacent structures (7).

Sullivan et al. (7) treated head and neck cancer, in addition to other tumours, with continuous IA infusion of methotrexate (MTX) together with the intramuscular administration of leucovorin every 6 h. This method consisted of the continuous arterial infusion of anticancer drugs through a surgically placed catheter in the superficial temporal artery by means of a small, portable, ambulatory infusion pump (Fig. 1). The arterial route was used to develop a high drug concentration in the tumour site. Partial or complete responses (CRs) were observed in 10 of 18 patients treated.

The first trial comparing IA chemotherapy to radiotherapy was conducted at the Institut Gustave-Roussy in 1965 (8). This trial sought to compare the combination of IA infusion chemotherapy and radiotherapy with radiotherapy alone in advanced (T4) cancers of the oral cavity and oropharynx. MTX was administered through a catheter in the superficial temporal artery. Tumour regression was far greater with the combination treatment: 40% compared with 10% for radiotherapy alone. The median survival rate was 6 months in the group receiving radiotherapy alone and 9 months in those receiving the combination therapy.

Clinical investigations of IA chemotherapy for advanced or recurrent head and neck cancer were carried out across the globe in the 1960s. It appears that the dramatic and CR sometimes noted with IA chemotherapy in marked contrast to usual results from systemic chemotherapy greatly encouraged investigators (9). In addition to MTX, 5-fluorouracil (5-FU), bleomycin (BLM), mitomycin-C and cisplatin as well as combinations of them were subsequently investigated.

**IA chemotherapy as induction chemotherapy**

Arcangeli et al. (10) conducted a randomized trial on induction IA chemotherapy to ascertain whether a prior reduction in tumour size by drugs could affect the final outcome of tumours treated with radiation. One hundred and forty-two patients with head and neck cancer (oropharynx, maxillary antrum and intra-oral) were randomized for the study. In 72 cases, irradiation was preceded by the continuous IA infusion of MTX; the other 70 patients were treated with radiotherapy alone. The overall 5-year survival was 43% in the combined treatment group and 25% in the group treated with radiation alone ($P < 0.05$). However, when analysed separately, the difference was statistically significant only in oral cavity tumours (5-year survival of 54% in the combined modality group versus 27% in the control group), although local control rates after both single and combined modalities were not significantly different from those of oropharynx and maxillary antrum tumours.

A multicentre randomized trial was also conducted by the Head and Neck Group of the European Organization for Research and Treatment of Cancer (EORTC) to evaluate the role of preoperative IA chemotherapy on survival in patients with tumours of the oral cavity and oropharynx (11). Between 1978 and 1984, 222 eligible patients were randomized between surgery and preoperative IA chemotherapy. The latter group received vincristine + BLM from a catheter placed retrograde into the external carotid artery from the superficial temporal artery. The overall survival showed a statistically significant difference ($P = 0.048$) for the floor of mouth but not for the posterior oral cavity or oropharynx groups. In the floor of mouth group, median survival in the preoperative IA chemotherapy arm...
was estimated at 7 years, compared with 3 years in the surgery arm. In the posterior oral cavity and oropharynx groups, median survival was estimated at 3 years in both treatment arms. This trial was the only one to show that the use of IA administration in one particular location had a significant impact on survival. However, this result was not what the investigators working on IA chemotherapy for head and neck cancer had expected.

Despite almost three decades of experience, the use of IA chemotherapy for the treatment of head and neck cancer was not universally accepted. The overall reported response rates were not substantially different from the therapeutic results obtained with systemic therapy. The additional complications associated with establishing and maintaining arterial access have further dampened enthusiasm for this approach (12). Most studies involved percutaneous catheterization of the external carotid with or without implantable infusion pumps and indwelling catheters, and this remained problematic because of the risk of infection and thrombosis.

The introduction of IA chemotherapy to Japan

IA chemotherapy was introduced, mainly for the treatment of maxillary sinus cancer, in 1960s through to the early 1980s in Japan as maxillary sinus cancer accounted for ∼30% of the cancers arising in the upper aerodigestive tract at that time. The overall survival for patients with maxillary sinus cancer was reported to be 30–40% in the 1960s. Therefore, a new strategy was needed for what was, at that time, a burning issue. Moreover, maxillary sinus cancer is particularly suited to IA chemotherapy as it tends to be encompassed mostly within the territory of the internal maxillary artery. Further, technical difficulties associated with the infusion procedure is less of a problem in patients with sinus cancer as the tip of the catheter usually only needs to be below the take-off of the internal maxillary artery and occasionally below the take-off of the facial artery (13). IA chemotherapy was investigated all over Japan in 1960s following the Sullivan report on continuous IA infusion (7).

Sato et al. (14) at Tokyo University developed a multidisciplinary approach known as ‘trimodality therapy’ (Fig. 2). Their strategy was based on continuous arterial infusion of 5-FU, concomitant radiation and cleaning of the antrum with a curette and forceps, followed by organ preservation surgery. A Teflon catheter was inserted retrograde through the superficial temporal artery under local anaesthesia so that the tip of the catheter was located at the bifurcation of the internal maxillary artery. The position of the tip of the catheter was determined by slow injection of patent blue violet. At the same time, the canine fossa was widely exposed by a sublabial incision, and the anterior wall of the maxillary sinus was then removed as far as possible. The antrum was kept open by packing with gauze. 5-FU (250 mg/body per day) was infused by an electrically driven pump via a catheter inserted from the superficial temporal artery for 1 h per day. Just after the infusion of 5-FU, 7000 rads of radiotherapy was administered. The degree of tumour regression was observed during the chemotherapy and radiotherapy and ascertained histologically by taking biopsy specimens once a week from the opened window. In addition, the necrotic tumour mass in the antrum was sucked out. Sato stated that the practice of thoroughly cleaning out the necrotic mass was indispensable to attaining good results. After 1968, the radiation dose was decreased gradually because of radiation-induced eye problems, oedema and necrosis of soft tissue after the therapy. From 1972 to 1974, the dose of radiation was 20 Gy/10f, and the 5-year overall survival at that period was ∼50%. Sato mentioned that the radiation therapy was used to facilitate cleaning and curettage of the antrum by softening the tumour and to activate local immune reaction rather than to sterilize malignant cells. They reported a higher 5-year survival together with a higher preservation rate of the maxilla than the results reported prior to that time in Japan.

Many investigators were encouraged by this success and tried this treatment method. However, other institutions did not achieve the same excellent results as Sato. Reasons for this discrepancy in results included frequent catheter-related complications; inadequate selectivity in some cases (therefore, some cases appeared to show an excellent

Figure 2. Diagram of treatment method reported by Sato et al. (14), reproduced with permission from John Wiley and Sons.
effect, while others did not; progressive scarring of the upper lip and cheek; and the need for daily treatment, such as sucking out the necrotic tumour mass. This latter treatment caused significant pain to patients and required a lot of time and energy on the part of the head and neck surgeons. Wide resection and reconstructive surgery have recently become popular, resulting in a decrease in the popularity of trimodality therapy. However, modifications of the trimodality therapy by Sato have been used as organ preservation therapy until recently (15–17), with Nishino, a direct heir of Sato’s methods, reporting excellent results. His method includes 20 Gy irradiation, 5-FU IA infusion and minimally invasive surgery. In 97 patients with squamous cell carcinoma (SCC) of the maxillary sinus, the 5- and 10-year overall survival rates were 76 and 70%, respectively (17). In addition, a few centres in Europe adopted this treatment modality and reported good results (18–20).

Mitani et al. (21) at the National Cancer Institute in Tokyo reported the results for maxillary sinus cancer from their institution. From 1970 to 1980, 78 patients with maxillary sinus cancer were treated with radiotherapy together with IA chemotherapy with 5-FU and reduction surgery. During that period, local control and overall survival rates at 5 years were 75.6 and 43.1%, respectively. From 1981 to 1990, 33 cases were treated with preoperative radiotherapy, IA chemotherapy with 5-FU and en bloc tumour resection. Local control and overall survival rates were 93.9 and 69.7%, respectively. From 1991 to 1998, the extent of each tumour was precisely evaluated by computed tomography and magnetic resonance imaging, so radical surgery became the mainstay of the treatment. During that period, 40 cases were treated by preoperative radiotherapy and en bloc resection without IA chemotherapy. As a result, local control and overall survival rates were 82.5 and 61%, respectively. This was lower than the previous period, although the difference was not significant. This rate shows that IA chemotherapy has some effect with regards to local control. In fact, local recurrence was seen supero-posteriorly in all cases during the last period. The tumour invasion supero-posteriorly from the maxillary sinus is difficult to remove completely. This, therefore, shows that IA chemotherapy may have a role in controlling tumour invasion supero-posteriorly from maxillary sinus cancers.

As mentioned above, IA chemotherapy has been mainly applied for maxillary sinus cancer and has a role as one of the treatments applied in a multidisciplinary approach. The treatment results for maxillary sinus cancer seem better than those of other countries; the 5-year overall survival rates for maxillary sinus SCC in Japan were reported to be 57–78.4% (17,22–24), whereas those in Western countries were reported to be 29.3–49% (25–27). According to these results, IA chemotherapy might have played a positive role. However, treatment methods differ from institution to institution and there has been no prospective multi-institutional trial. Therefore, it is difficult to evaluate the efficacy of IA chemotherapy.

**Superselective IA infusion**

Advances in vascular radiology techniques enabled superselective IA infusion to the head and neck structures in 1980s. ‘Superselective IA infusion’ has been generally used when IA infusion is performed via a catheter inserted into a branch of the external carotid artery, such as the maxillary artery, facial artery or superior thyroid artery. Recently, the catheter has been inserted further into the more peripheral branches. Using a newly developed coaxial catheter system, the MD Anderson group studied the effects of IA chemotherapy on 41 patients with advanced recurrent or untreated head and neck tumours. All patients were treated with short-term (1–1.5 h) IA infusions of cisplatin into the external carotid artery via the femoral arterial route using the Seldinger technique, achieving an immediate tumour response rate of 29.3% (28). Using more careful superselective catheterization, they then treated 24 patients with advanced paranasal sinus tumours by combined superselective IA and systemic chemotherapy, yielding an immediate satisfactory tumour response rate of 91%. Significantly, eight patients avoided craniofacial surgery as a result of their response to treatment (29).

In Japan, Imai et al. (30) and Korogi et al. (31) introduced superselective IA infusion using the Seldinger’s techniques for head and neck cancer. A microcatheter was placed in the target arteries, selected according to the location of the tumour, via the femoral artery. Hirai et al. (32) described the theoretical advantages of their methods as follows: (i) catheterization is easy and safe due to improvements in catheters and angiographic units; (ii) there is exact identification of feeding vessels; (iii) even when the tumour has multiple feeding arteries, all feeders can be infused easily at one session and (iv) patients were completely free from the need for treatments between sessions.

One of the concerns about IA chemotherapy is the risk of catheter-related neurologic complications. Robbins reported that 7 (3.3%) of 213 patients developed neurologic sequelae during treatment by RADPLAT protocol, consisting of the IA delivery of cisplatin with systemic neutronulization by i.v. sodium thiosulphate, and concurrent radiotherapy, in the University of Tennessee, Memphis (33). In a multi-institutional setting (RTOG 9615), Grade 3–4 neurologic toxicity was observed in 5 (8.2%) of 61 patients. This included two patients (3.3%) with clinical evidence of a transient ischaemic attack, although they made a complete recovery, two patients (3.3%) who developed peripheral neuropathy and one patient (1.6%) who had a cerebrovascular accident with permanent sequelae (34). In a Dutch trial, neurological toxicity Grade 2 or more, i.e. transient ischaemic attacks, was observed in 8 (6.8%) of 118 patients treated by RADPLAT. One of the eight patients had a cerebrovascular accident with full recovery (35). Homma et al. (36) reported their early experiences of RADPLAT. Of 43 patients treated between 1999 and 2003, two patients had Grade 3–4 neurologic toxicities; however, they treated 236 patients as of March 2015 and no patient other than the two mentioned above showed Grade 3–4 neurologic toxicity. According to previous reports, catheter-related neurologic complications were supposed to occur in 1–6% of all patients receiving RADPLAT. However, experienced centres appeared less likely to encounter catheter-related neurologic complications.

Hattori et al. (37), Tohnai et al. (38), Fuwa et al. (39) and other investigators reported superselective infusion therapy via the superficial temporal artery. Under fluoroscopic guidance, an angiographic catheter was inserted in a retrograde manner into the main feeding artery of the tumour via the superficial temporal artery. Superselective IA infusion via the superficial temporal artery seems to be technically simple and rarely leads to cerebrovascular accidents. However, catheter-related complications, such as obstruction of the vessel, infection and displacement of the catheter, sometimes occur. In addition, this method cannot address tumours that are fed by multiple arteries. Therefore, this technically simple technique is only useful if the tumour is small and fed by one artery, such as small tongue cancers or T3 maxillary sinus cancers.

Significant advances in vascular radiology techniques and new devices, such as fluoroscopy units and angiographic catheters, make possible safe, accurate and repeated superselective IA chemotherapy (29,40,41). These techniques and tools continue to be improved, making it possible to perform safer and more accurate superselective IA chemotherapy than ever before.
High-dose IA cisplatin chemotherapy

The biggest advantage of IA infusion is that the drug is considered to be distributed at high concentrations in the regional artery supplying the tumour during initial circulation after the dose. When the drug reaches the heart, it is detoxified or excreted before the next circulation as it has passed through the liver and kidneys. As a result, the blood concentration of the drug during the next circulation does not differ from the levels achieved after i.v. infusion (42).

Cisplatin has been a key chemotherapeutic drug for patients with head and neck cancer. In cancer chemotherapeutics, there is evidence that drug resistance can be overcome by increasing drug dosage. However, the conventional dose of cisplatin is 100 mg/m² per cycle, and administration of 100 mg/m² of cisplatin is repeated only every 3 weeks due to renal and gastrointestinal toxicities. To date, clinical trials using cisplatin in doses above this level have only been possible by the simultaneous administration of sodium thiosulfate.

Clinically, it is possible to deliver higher concentrations of cisplatin through pharmacological and technical manipulation. One strategy is through IA delivery. The relative advantage \( R_t \) of IA infusion (relative to i.v. infusion of the same dose and schedule) is defined by the equation: \( R_t = 1 + (\text{plasma clearance}/\text{tumour plasma flow}) \). The greater the plasma clearance of the drug and the smaller the tumour plasma flow, the greater the advantage of injecting the drug via the IA route. All of the benefit of an IA infusion occurs with the first pass of the drug through the tumour bed, as once the drug enters venous circulation, subsequent tumour exposure is equivalent, due to recirculation, whether the drug entered systemic circulation via an IA or an i.v. injection (43).

In order to increase the therapeutic advantage of cisplatin, one must either decrease tumour plasma flow or increase plasma clearance (44). The former can be accomplished by giving the IA injection into as small an artery as possible. In the case of cisplatin, the latter can be accomplished by using the neutralizing agent thiosulfate (45). Thiosulfate reacts covalently with cisplatin to produce a complex that is still soluble but totally devoid of either toxicity or antitumour activity (46). When this neutralization occurs in the plasma, it effectively increases the ‘clearance’. The extent of the reaction is a function of the concentration of both agents (46). Thiosulfate is not a very potent neutralizing agent, and molar thiosulfate/cisplatin ratios in excess of 10 are required before the reaction is fast enough to contribute significantly to the clearance of cisplatin (47). Thiosulfate has been used extensively at the University of California, San Diego, in conjunction with intraperitoneal chemotherapy for ovarian carcinoma (45,48), and pharmacokinetic studies have demonstrated an additional important feature of its use (49). Thiosulfate is very non-toxic and extensively (>25-fold) concentrated in the urine, and the latter provides excellent protection against cisplatin-induced nephrotoxicity (50). When the kidneys are protected against toxicity, either with thiosulfate (51) or with large volumes of saline, the rest of the body will tolerate a doubling of cisplatin exposure. Thus, the ability of thiosulfate to selectively protect the kidneys reduces the requirement for cisplatin neutralization by thiosulfate in the plasma.

Superselective arterial infusion of high-dose cisplatin

Robbins et al. developed a specific concomitant chemotherapy protocol for head and neck cancer that employed the pharmacologic principles of IA cisplatin while capitalizing on the cisplatin-neutralizing agent sodium thiosulfate. In a Phase I study, it was determined that cisplatin could be safely administered to patients with advanced and recurrent head and neck cancer at a dose intensity of 150 mg/m² per week (52). In the next step, concomitant radiotherapy was added to the high-dose cisplatin infusion strategy. The regimen, referred to as RADPLAT, consisted of IA cisplatin (150 mg/m²) and a concurrent i.v. bolus of sodium thiosulfate (9 g) followed with 12 g over 12 h for a total of four times; and concomitant irradiation 180–200 cGy/fraction 35 times over 7 weeks (Fig. 3) (53,54).

The RADPLAT programme uses the rapid IA infusion of cisplatin and concurrent i.v. administration of thiosulfate. During the brief interval of the rapid IA infusion, the tumour is exposed to an extraordinarily high cisplatin concentration (~250 times higher than the peak plasma concentration following standard i.v. dosing). Due to the very high cisplatin/thiosulfate concentration ratio in the tumour bed and the slow rate of reaction between cisplatin and thiosulfate, little neutralization is expected in the tumour (51). However, once the cisplatin passes through the tumour and reaches the plasma, it is diluted into the blood volume, and its concentration falls relative to the high concentration of thiosulfate in the plasma. This favours neutralization and effectively increases plasma clearance.

Between 1993 and 1997, 213 patients with Stage III–IV disease were treated with RADPLAT at the University of Tennessee, Memphis (33). Ninety-four patients (44%) had T4 disease, 102 (47%) had T3 disease, 15 (7%) had T2 disease and 2 (1%) had T1 disease (both of these patients had N3 nodal disease), while 28.6% of patients had Stage III disease and the remaining 71.4% had Stage IV disease. Of the 213 patients entered into the treatment programme, a CR in the primary site was obtained in 171 (80%). With a median follow-up of 30 months (range: 16–69 months), the Kaplan–Meier plot projections for overall and cancer-related 5-year survival were 38.8 and 53.6%, respectively, whereas disease control above the clavicle was 74.3%.

To determine the feasibility of RADPLAT for head and neck SCC in a multi-institutional setting, a subsequent trial was conducted (Multi-RADPLAT) for patients with T4 SCC of the oral cavity, oropharynx, hyopharynx or larynx. Between May 1997 and December 1999, 67 patients from three experienced and eight inexperienced centres were enrolled, of whom 61 were eligible for analysis. The results

![Diagrammatic illustration of the drug delivery technique used in the RADPLAT programme](https://example.com/diagram.png)

**Figure 3.** Diagrammatic illustration of the drug delivery technique used in the RADPLAT programme [54]. I.A. DDP, intra-arterial cisplatin; I.V. S₂O₃, intravenous sodium thiosulfate.
indicated that Multi-RADPLAT was feasible (i.e. three or four infusions of IA cisplatin and a full dose of radiation) in 53 (87%) patients. The CR rate was 85% at the primary site and 88% in the nodal regions, with an overall CR rate of 80%. At the median follow-up of 3.9 years for patients alive (range: 0.9–6.1), the estimated 1-year and 2-year local-regional tumour control rates were 66 and 57%, respectively. The estimated 1-year and 2-year survival rates were 72 and 63%, respectively. The estimated 1-year and 2-year disease-free survival rates were 62 and 46%, respectively. The corresponding rates of Grade 4 and 5 toxicities at the experienced and the inexperienced institutions were 14 and 0% versus 47 and 4%, respectively. The conclusion of this study was that the intensive RADPLAT treatment regimen for head and neck cancer is both feasible and effective in a multi-institutional setting (34).

Yokoyama et al. (55) first reported RADPLAT in Japan in 1998. They reported that large tumours were resolved using this therapy and high-dose weekly cisplatin infusion did not cause any serious side effects, which surprised Japanese head and neck oncologists. Since then, IA chemotherapy has gained recognition and renewed popularity in Japan as its long history of use made it easy to accept.

Based on the promising results of RADPLAT reported by Robbins et al. (53,56), a randomized trial was conducted in the Netherlands comparing RADPLAT with i.v. chemoradiation therapy (35). Two hundred and thirty-six patients from five hospitals with (functional) inoperable head and neck cancer were randomly assigned to receive radiotherapy (70 Gy/35 fractions/7 weeks) combined with either four courses of IA cisplatin on Days 2, 9, 16 and 23 or i.v. cisplatin on Days 1, 22 and 43. After a median follow-up of 7.5 years, no differences in locoregional control or overall survival were observed between the treatment arms. The rate of renal toxicity Grade 2 or more was 9% in the i.v. arm compared with 1% in the IA treatment arm (P = 0.0001). Late dysphagia was also worse in the i.v. arm (log-rank P = 0.014). Renal toxicity was lower and neurological toxicity was higher in the IA arm. They concluded that IA cisplatin did not improve tumour control compared with i.v. administrated cisplatin. However, there continues to be serious questions about the high proportion of patients in the trial who received the less-effective technique of bilateral infusion as well as the fact that >60% of patients had oropharyngeal cancer. Oropharyngeal cancer is generally considered to be more sensitive to chemotherapy and radiotherapy than other head and neck cancers apart from nasopharyngeal cancer. In addition, HPV was considered to be related to the development of cancer in many of the patients with oropharyngeal cancer in this trial. They were expected to have a good prognosis even if they received less-intensive therapy. It is, therefore, possible that patient selection and catheterization methodology influenced the results of this trial (57). Although RADPLAT was beneficial for patients with relatively large tumours (>30 cm³) not extending across the midline in the subgroup analysis (35,58), no follow-up on RADPLAT was undertaken worldwide, except Japan, due to the results of the Dutch trial.

**Site-specific results of IA chemoradiotherapy**

Here, we will discuss the treatment results of IA chemoradiotherapy as a definitive therapy without surgery for patients with SCC in various sites in the head and neck.

**Nasal cavity and paranasal sinuses**

With regards to maxillary sinus cancer, Homma et al. reported 54 cases treated by RADPLAT. The 5-year local progression-free and overall survival rates were 65.8 and 67.9% for all patients, respectively (23). No patient died as a result of treatment toxicity or experienced a cerebrovascular accident. Osteonecrosis (n = 5), brain necrosis (n = 1) and ocular/visual problems (n = 14) were observed as late adverse reactions. The Dutch trial found that there were significantly higher local control rates with IA treatment than with i.v. treatment for large (>30 ml) lateralized tumours (35). Maxillary sinus cancer is generally large and lateralized, although the Dutch trial did not include any cases of maxillary sinus cancer. Thus, it appears to be suited to treatment with RADPLAT therapy. Indeed, several good results achieved by the use of RADPLAT have been reported in Japan (22,24,59,60). As for nasal cavity and ethmoid sinus cancer, Homma et al. (61) also reported that the primary disease was successfully controlled by RADPLAT in seven of eight patients. The remaining patient developed distant metastasis without primary site recurrence. With regards to late adverse reactions, brain necrosis (Grade 2) was observed in one patient. Three patients experienced ocular/visual problems (Grades 3–4), and all of them required orbital exenteration if surgery were indicated. Other than the above, angiography in one patient with T4a ethmoid cancer revealed that the tumour was not supplied by the external carotid system at all, and she subsequently received i.v. chemoradiotherapy.

**The base of tongue**

Kawaguchi et al. (62) performed RADPLAT for one patient with T2 the base of tongue (BOT) cancer and four patients with T3 disease. Locoregional control was achieved for all five patients. Kano et al. (63) treated 13 patients with T2–4a BOT cancer with RADPLAT and reported 5-year local control and overall survival rates of 92.3 and 90.9%, respectively, for all patients. Further, all of the surviving patients achieved normal swallowing without a feeding tube and normal speech without tracheostoma after treatment.

The standard therapy for locally advanced BOT cancer is chemoradiotherapy or surgery. RADPLAT can provide another option in centres with a good deal of experience with RADPLAT.

**Larynx and hypopharynx**

With regards to laryngeal cancer, RADPLAT has shown good results, achieving 80–100% local control rates (64–67). Laryngeal necrosis does, however, develop in some patients. Yokoyama and Furukawa (67) reported that 2 of 40 patients with laryngeal cancer treated with RADPLAT developed laryngeal necrosis. They concluded that the cisplatin dose should be 50–100 mg/m² per cycle. Indeed, other investigators have reported using cisplatin at a dose of 75–100 mg/body (65,66). I.V. chemoradiotherapy also showed good local control rate in these cancers. Therefore, the indication of RADPLAT for laryngeal cancer might be limited.

Hypopharyngeal cancer often has been analysed together with laryngeal cancer. However, the incidence of lymph node metastasis is higher than that in laryngeal cancer, and the prognosis is much worse. Samant et al. (68) reported 25 patients with Stage III/IV pyriform sinus treated with RADPLAT. The 5-year overall survival and locoregional control rates were 23% and 88%, respectively. Nomura et al. (69) treated 45 patients with T2N0 or worse hypopharyngeal cancer with RADPLAT. Three, 7, 21 and 12 patients were diagnosed with Stage II, III, IVA and IVB cancer, respectively. During the median follow-up period of 34 months, the 3-year overall survival and the 3-year local control rates for all patients were 52.2 and 81.6%, respectively. No patient died because of treatment toxicity. In terms of
Grade 4 toxicities, cerebral infarction ($n=1$) and laryngeal necrosis ($n=1$) resulting in laryngectomy were observed.

Reported results have shown that the overall survival rates achieved using RADPLAT were less than impressive, although the local control was generally good. Furusawa et al. (70) assessed the indications for RADPLAT in patients with hypopharyngeal cancer. The 5-year overall survival was 51.3%, and the 5-year local control was 81.6% for all patients. A statistically significant difference in the 5-year overall survival was noted between patients with N0-1 ($n=14$) and N2b-3 disease ($n=27$). One-half of deaths were observed to be the result of distant metastasis. The 5-year local control and overall survival were significantly better in patients with unilateral than in those with bilateral primary tumours. All the patients with T4b disease ($n=3$) died of disease within 2 years. According to the results, they concluded that indications for RADPLAT in patients with HPC should be defined as patients with unilateral tumours staged as T3-4a and N0-1.

Oral cavity
Mitsudo et al. (71) reported their experiences of retrograde superselective IA chemotherapy and concurrent radiotherapy (60 Gy). One hundred and twelve patients with Stage III and IV oral cancer underwent superselective IA chemotherapy (docetaxel, 10 mg/m² per week, total 60 mg/m²; cisplatin, 5 mg/m² per day, total 150 mg/m²) and concurrent radiotherapy (total of 60 Gy) for 6 weeks. Primary site CR was achieved in 98 (87.5%) of 112 cases. Five-year survival and local control rates were 71.3 and 79.3%, respectively. Grade 3 or 4 mucositis occurred in 92.0% of patients. Their results were impressive, but concerns remain regarding late toxicities, such as osteoradionecrosis of the mandible, severe mouth dryness and atrophy of the tongue, due to the high-dose radiation therapy for the oral cavity and IA chemotherapy. Nishioha et al. reported on four patients with advanced tongue cancer who rejected radical surgery and were given superselective IA infusions of cisplatin (100–120 mg/m² per week) with simultaneous i.v. infusion of thiosulfate to neutralize cisplatin toxicity and conventional external beam radiotherapy (30–50 Gy). High-dose-rate radiotherapy and tracheostomy were also performed under general anaesthesia to avoid severe late toxicities (72). During a mean follow-up period of 35 months, one patient died of distant metastasis, while the rest are disease free at present. Locoregional control was obtained for all patients. Although atrophy is observed in treated tissue, tongue mobility is only slightly impaired and the patients have no complaints. Further studies are required to establish the indications, long-term outcome and possible late adverse effects of this treatment. In addition, the treatment of Mitsudo and Nishioha might require more time and effort for both patients and medical staff than surgery.

Temporal bone
The prognosis for advanced stage temporal bone cancer is expected to be poor even if surgery is indicated, while the prognosis when nonsurgical approaches, such as radiotherapy or with without chemotherapy, are employed have been found to be disappointing (73–75). There are, however, several promising reports regarding RADPLAT (76–78). Sugimoto et al. (77) reported five patients treated with RADPLAT. Three patients remain alive without local recurrence (mean survival, 28 months), one patient died of distant metastasis without local recurrence after 19 months and one patient remains alive with local recurrence. Fujiwara et al. (78) also reported 13 patients (T3: 1 patient and T4: 12 patients) treated with RADPLAT. The overall survival and progression-free survival rates at 2 years were 58.7 and 53.8%, respectively. No late-phase adverse effects or adverse effects due to catheterization were observed. They concluded that RADPLAT can be a treatment option for locally advanced carcinomas of the external auditory canal and middle ear.

Future perspectives—a Japanese clinical trial for maxillary sinus cancer
The JCOG Head and Neck Cancer Study Group began a multi-institutional prospective RADPLAT trial in April 2014 (79) (Fig. 4). A dose-finding and efficacy confirmation trial is being conducted to evaluate the efficacy and safety of the superselective IA 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 or fewer cycles in the dose-finding phase, will be enrolled from 19 institutions within a 5-year period in the efficacy confirmation phase. The primary end point of the dose-finding phase is dose-limiting toxicities. The primary end point of the efficacy confirmation phases is the 3-year overall survival, which will be compared with the data obtained in the observational study undertaken by the JCOG Head and Neck Cancer Study Group. This trial was registered at the UMIN Clinical Trials Registry (https://www.umin.ac.jp/ctr/) under Trial No. UMIN000013706.

Conclusion
IA chemotherapy, particularly superselective IA infusion of high-dose cisplatin with systemic neutralization by i.v. sodium thiosulfate, is a theoretically attractive approach to the treatment of advanced head and neck cancer. However, i.v. chemoradiotherapy has also showed excellent results, and the recent increase in the incidence of HPV-related cancer, which has a good prognosis, may have masked any differences in efficacy between these two treatment modalities. Further, RADPLAT needs a considerable amount of time and effort on the part of medical staff. Therefore, the indications for RADPLAT...
should be refined and a prospective trial should be conducted in the future to establish the indications and confirm the efficacy of RAD-PLAT as well as to better define the patient group.

Funding
This research is supported by the Practical Research for Innovative Cancer Control (15ck0106137h0002) from Japan Agency for Medical Research and development, AMED.

Conflict of interest statement
None declared.

References