Chapter 1. Introduction

Intra-arterial Chemotherapy for Head and Neck Cancer

In head and neck cancer, treatments and prognoses differ depending on the site, and especially for cancer of paranasal sinuses, oropharynx, hypopharynx, and larynx, a well-balanced treatment between curability and function preservation is necessary Intra-arterial (IA) chemotherapy is a general term for a treatment with intensive anticancer drug administration using an arterial catheter. In the field of head and neck cancer where the impairment of quality of life is significant due to radical surgery from a functional and cosmetic point of view, the treatment is considered to be useful. In this book, we deal with the RADPLAT protocol which is a mainstream treatment in Japan and for which the most evidence is currently being accumulated. This treatment is expected to largely outperform standard treatments when cases are carefully chosen and appropriate techniques are used.

Head and Neck Cancer

Head and neck cancer is a generic term for malignant tumors originating from nasal cavity and paranasal sinuses, oral cavity, pharynx, larynx and so on. Treatments and prognoses differ depending on the site, and among these sites, for cancer of nasal cavity and paranasal sinuses, oropharynx, hypopharynx and larynx, IA chemotherapy is thought to be effective. According to the 2008 Vital Statistics of Japan, head and neck cancer accounts for 4.3% of all cancers, and the prevalence rate is 25.4 out of 100,000. The numbers have been steadily increasing since the 1970s. There are differences in the ratio of men to women in each affected area, in cancer of nasal cavity and paranasal sinuses it is 1.3, while it is 22.0 for laryngeal cancer which means there are overwhelmingly more men. According to the Head and Neck Cancer Registry in Japan, the most common primary site is the oral cavity, followed by the larynx, hypopharynx, oropharynx, nasopharynx, nasal cavity, and maxillary sinus. In histological types, **squamous cell carcinoma** is the predominant in the oral cavity and oropharynx and hypopharynx, accounting for more than 95% of cases, while it is only about 70% in the nasopharynx and maxillary sinus, and decreases to 35% in the nasal cavity. Malignant lymphoma is seen in the nasopharynx, malignant melanoma is often seen in the nasal cavity, and various histologic types occur in the maxillary sinus.

Among these head and neck cancers, sinonasal, hypopharyngeal, and laryngeal cancers occur in the area which is responsible for important functions for social life such as speech, mastication, taste and smell. This area also maintains facial appearance and forms facial expressions. Even if curative surgery is possible, it results in the significant impairment of quality of life. On the other hand, this is where the majority of squamous cell carcinoma responds well to chemoradiotherapy, making it one of the most useful areas for IA chemotherapy balancing curability and function preservation.

IA Chemotherapy

IA chemotherapy is a term for treatments with intensive administration of an anticancer drug to a tumor using an arterial catheter, and is mainly used for locally advanced head and neck cancer, of which there are various techniques. Since anticancer drugs are infused selectively through the feeding arteries of the tumor, it is highly effective in treating a localized area, unlike chemoradiotherapy. This is a well-balanced treatment between curability and function preservation especially for locally advanced cancer. In the field of head and neck cancer where the impairment of quality of life is significant due to radical surgery from a functional and cosmetic point of view, this treatment is considered to be a useful alternative therapy not only for unresectable cases but also for resectable advanced cancer. The approaches include the femoral artery and the superficial temporal artery, and anticancer drugs include platinum-based drugs, taxanes, and pyrimidine fluoride. The dosage varies depending on facilities; in some facilities a large amount is intra-arterially injected, while in others a small amount is used before performing resection. Depending on the types of anticancer drugs, antidotes can be administered simultaneously. Radiotherapy is usually performed concurrently with IA chemotherapy. Although there are various techniques of IA chemotherapy, being intra-arterial and locally focused chemotherapy is the common denominator.

RADPLAT

In this book, we provide a detailed explanation of the RADPLAT protocol which is a mainstream treatment in Japan and for which the most evidence is currently being accumulated. RADPLAT (radiation + platinum) is a method of IA infusion developed by Robbins et al. in 1992. They adopted the Seldinger technique as a way to access the artery and injected a high-dose anticancer drug **superselectively** into the tumor's feeding artery via an arterial catheter. At the same time, a **neutralizing agent** was administered intravenously to remove the anticancer drug from the systemic circulation, and external beam irradiation was performed in parallel. This treatment for locally advanced head and neck cancer resulted in significantly more favorable outcomes than conventional treatments, and therefore it is considered to be widely performed IA chemotherapy in Japan.

The anticancer drug used for RADPLAT is **cisplatin**, a platinum-based drug. Cisplatin is a complex ionic form of the heavy metal platinum and is categorized as a heavy metal alkylating agent analogue. The antitumor effect is concentration-dependent fast-acting and slow-acting (Type Ib, Shimoyama classification) with small dependence on the cell cycle mainly due to the cross-link reaction of DNA strands. That is, the therapeutic effect of cisplatin infusion into the tumor's feeding artery is largely dependent on the blood concentration at the first passage, and the effect after the agent passes through the tumor and enters the systemic circulation is quite limited.

Taking advantage of this feature, by intravenously administrating **sodium thiosulfate**, a neutralizer of cisplatin, in parallel with IA infusion, the main therapeutic effect on a tumor can be maintained while the side effects during systemic circulation can be reduced. From a different perspective, this means that each cisplatin dosage can be significantly increased while keeping the side effects within an acceptable level. In combination with a superselective technique of IA infusion into the feeding artery using a microcatheter, this treatment enabled the increase of cisplatin concentrations in the tumor to tens of times more than conventional systemic chemotherapy. Drug resistance to cisplatin has been shown to be penetrated by

increasing the concentration. Furthermore, cisplatin has a radiation sensitizing effect, so that by giving external beam irradiation with the agent remaining in the tumor, higher therapeutic effects are expected. In other words, cisplatin is highly effective in treating squamous cell carcinoma, and can be detoxified with a neutralizing agent, which makes it possible to increase the dosage, and synergistic effects with radiotherapy are expected. Cisplatin is the key drug for RADPLAT.

Indication of IA Chemotherapy

The indications of IA infusion are for locally advanced head and neck cancers, specifically cancer of nasal cavity and paranasal sinuses , oropharynx, hypopharynx, and larynx. Several conditions are required even within this group. Originally the development of treatment for locally advanced head and neck cancer had been carried out separately for each primary site, including the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, oral cavity, and larynx, due to the differences in pathogenesis and prognosis. In IA chemotherapy, treatment outcomes vary depending on the sites of head and neck cancer and on the size and localization of the primary lesion. The indications should be carefully selected.

Good indications for deriving the greatest benefits from IA chemotherapy include:

- Previously untreated
- pathology: squamous cell carcinoma
- Candidate must be of age to complete the treatment (65 years old or younger, 75 or younger if in good general condition)
- Tumor localized on one side
- large tumor (volume of 30mL or larger)
- No nutrition from the internal carotid artery system

The primary sites which meet these criteria are the tongue, root of tongue, maxillary gingiva, maxillary sinus and nasal cavity. In particular, the maxillary sinus is regarded as the best indication for the IA chemotherapy.

Maxillary sinus cancer accounts for 3.6 % of all head and neck cancer, and squamous cell carcinoma is the most common, accounting for 77%. Early detection is difficult because there are few subjective symptoms in the early stages, and when detected, locally advanced cancer (T3 or higher) is often already present. On the other hand, there is little lymph node metastasis and distant metastasis, therefore local control is likely to directly affect the prognosis. Partial or total maxillectomy is significantly associated with postoperative dysfunction and decreased cosmetic quality of life. Hence IA chemotherapy is considered to be a more effective treatment that provides a high therapeutic efficacy in the localized area in a noninvasive manner.

In hypopharyngeal cancer, distant metastases often develop later even after the primary tumor has been controlled, thus a careful decision should be made on the indications. Distant metastasis is out of indication, while up to N2 cervical lymph node metastasis is within the indication.

Essential Points on IA Chemotherapy for Head and Neck

Trans-arterial administration of anticancer drugs via a catheter, known as “intra-arterial chemotherapy” in a broader sense, is used not only for head and neck cancer but also for the liver, bladder, uterus, breast, metastases, and other sites. Some readers may already have experience in the treatment. However, RADPLAT performed on head and neck cancer is fundamentally different from these areas. Physicians, including interventional radiologists, head and neck surgeons, and radiation oncologists who are involved in the treatment should be familiar with the following key points. Especially interventional radiologists who already have knowledge of IA chemotherapy in other organs are strongly encouraged to read these points.

It is a Curative Treatment Rather than a Palliative One

IA chemotherapy in head and neck cancer is not a palliative treatment but a curative treatment. In some types of cancer, chemoradiotherapy is supposed to aim at reducing the size of the cancer, resulting in a longer prognosis and improved quality of life. In contrast, IA chemotherapy in head and neck cancer aims at **complete cure of cancer**.

Treat All the Feeding Arteries

To obtain a complete response all the feeding arteries must be treated. An understanding of anatomy is important for this reason. If there is even a single feeding artery that has not been infused with anticancer drug, the tumor component in the perfusion area will be treated with radiation only. It is difficult to cure a locally advanced head and neck squamous cell carcinoma with radiotherapy alone. To treat many feeding arteries in a limited time, preoperational review of the images (especially 3D-CTA) and thorough understanding of the anatomy based on postoperative review are essential.

Number of cycles Determines Prognosis

In this treatment, the anticancer drug is infused once a week for total of 4 to 7 times (JCOG (Japan Clinical Oncology Group) 1212). The number of cycles is highly correlated with the prognosis, as well as loss of feeding artery due to technical errors and discontinuation of the treatment due to complications must be avoided as much as possible.

Preservation of Feeding Arteries

The main causes of loss of feeding arteries are vasospasm and damage to the vessel wall caused by inappropriate catheter manipulation due to the lack of knowledge of vascular anatomy and blind procedure. The external carotid artery system where IA infusion is performed is full of anatomical variations, and is extremely prone to vasospasm. Blind or unintended operation without understanding the vascular anatomy can easily cause vasospasm, and repeated vasospasm results in blockage of the feeding arteries, which directly leads to treatment failure. The use of 3D-CTA to understand vascular anatomy, and the roadmap, tip shaping of microcatheter and microguidewire and vasodilator to minimize the risk of vasospasm are required.

Avoidance of Complications

The most predictable procedure-related adverse events during this treatment are cerebral thromboembolism and cranial nerve palsy, however most of them are the former and can be avoided by acquiring skill in preventive measures. This treatment does not cause complications related to dangerous anastomosis or feeding artery for cranial nerves unless a very intrusive procedure is performed. Most of the possible complications are thromboembolisms. Thromboembolism should be recognized with the distinction between thrombus, air embolus and plaque embolus, and it is necessary to be acquainted with preventive measures for each.

It is “Superselective”

Cisplatin exerts its therapeutic effect when exposed to high doses against tumors, requiring catheter manipulation techniques based on this premise. Antitumor effectiveness of cisplatin is primarily a DNA interstrand cross-link reaction and is less dependent on the cell cycle.

In other words, it is concentration-dependent, specifically fast-acting and slow-acting (Type Ib, Shimoyama classification). The effectiveness of IA infusion depends greatly on the blood concentration at the first passage. Ultimately, the optimal state is to achieve 100% local blood concentration of cisplatin by counteracting normal blood flow. Prolonged exposure to a low dose of cisplatin does not produce sufficient therapeutic effects on the tumor.

To Increase Local Cisplatin Concentrations

In order to deliver cisplatin to the tumor’s feeding artery at higher concentration with more efficacy, it is necessary to place the microcatheter close to the tumor. The external carotid artery system is rich in artery-to-artery anastomoses. Much of the tumor blood flow is diverted from multiple blood supply channels. In order to increase the concentration of cisplatin, perfusion pressure at the end of the feeding arteries must be sufficiently increased during the IA infusion. In theory, it should be possible to place the microcatheter at any depth in the feeding artery and maintain the perfusion pressure provided that the infusion speed is increased. However, in fact, the more proximal the catheter position, the more reflux occurs depending on the infusion speed. Back-flowed cisplatin does not contribute to IA infusion and is lost unnecessarily. Therefore, microcatheters should be placed more distally to maintain high cisplatin doses in tumors and reduce the loss of cisplatin.

In the case of a drug (such as 5-FU) which the antitumor effect is less blood concentration-dependent and duration of exposure to the tumor is important, it is possible to block all nontarget arteries with embolization material such as platinum coils and place the catheter proximally to the feeding arteries for IA infusion. However, in case of cisplatin, proximal infusion itself does not function effectively for the above reasons. Although arterial redistribution technique is often performed in IA infusion for head and neck cancer, the main plan is the superselective catheter insertion (or catheter placement).

It is a Treatment of Last Resort

At this time, IA chemotherapy is the final resort of treatment for locally advanced head and neck cancer that is inoperable or where surgery was refused. The success or failure of this treatment is directly related to the patients’ prognosis, which is highly dependent on how the procedure is performed. Interventional radiologists need to keep this in mind when treating patients.