［原著］Carboplatin Selective Intra arterial Infusion Chemotherapy with Concurrent Radiotherapy on Cervical Lymph Node Metastasis in Squamous Cell Carcinoma in the Oral Region

Carboplatin Selective Intra-arterial Infusion Chemotherapy with Concurrent Radiotherapy on Cervical Lymph Node Metastasis in Squamous Cell Carcinoma in the Oral Region

Hai Kuang[1)], Hajime Sunakawa[1)], Akira Arasaki[1)],
Keiichi Arakaki[1)], Toshiyuki Nakasone[1)], Gosei Ueda[1)] and Masaki Gibo[2)]

[1)]*Department of Oral and Maxillofacial Functional Rehabilitation and*
[2)]*Department of Radiology, School of Medicine, University of the Ryukyus, Okinawa, Japan*

(Received on November 28, 2005, accepted on December 21, 2005)

ABSTRACT

In this retrospective study, we evaluated the effect of carboplatin (CBDCA) selective intra-arterial infusion chemotherapy with concurrent radiotherapy (SIACR) on cervical lymph node metastasis in patients with squamous cell carcinoma in the oral region, and determined the factors related to this effect. Twenty seven patients were enrolled with biopsy-proven squamous cell carcinoma of the oral region. They received CBDCA SIACR for cervical lymph node metastasis and underwent neck dissection. For all patients, 38 metastatic lymph nodes were diagnosed using a number of criteria. The short-axis diameters of lymph nodes were measured on CT images before and after SIACR. All metastatic lymph nodes were histologically classified into complete, good, or poor responses according to their histological features. Level I metastatic lymph nodes were classified as proximal or distal according to the position of the tip of the microcatheter in the feeding artery. In 9 of 27 patients, computed tomography angiography (CTA) was performed to evaluate the vascularity and extent of the primary tumor and metastatic lymph nodes. The reduction percentage of lymph node short-axis diameters was 0%-58.3% with a mean of 26%. Complete response nodes (36%±12%) showed a significant reduction in short-axis diameters compared with good (24%±15%) and poor (27%±11%) response nodes ($P<0.05$). In the proximal group, 0, 5(63%) and 3 (37%) lymph nodes exhibited complete, good and poor responses. In the distal group, 4 (44%), 5 (56%) and 0 lymph nodes exhibited complete, good and poor responses. The difference between the proximal and distal groups' histological response was statistically significant ($P<0.05$). No lymph nodes identified by CTA exhibited a poor response. A correlation between reduction in short-axis diameters of lymph nodes and histological responses was demonstrated in which reduction rates increased with histological response. Findings indicated that histological response was greater for patients in whom the tip of the microcatheter was placed distal to the branching site of the ascending palatine artery. The group with confirmed contrast medium transport to the lymph node metastasis by CT angiography showed a better therapeutic effect, highlighting the importance of confirmation of drug transport by CT angiography. *Ryukyu Med. J.*, 24(3,4) 127~136, 2005

Key words: Selective intra-arterial infusion chemotherapy, Cervical lymph node metastasis, Carboplatin, Squamous cell carcinoma, Oral region

INTRODUCTION

One of the most important factors influencing prognosis in the treatment of squamous cell carcinoma in the oral region is the presence or absence of cervical lymph node metastasis. For improvement of treatment results, the most important issue is control of cervical lymph node metastasis as well as control of the primary lesion. Thus, accurate diagnosis of cervical lymph node metastasis and establishment of diagnosis-based selection criteria for appropriate treatment can potentially lead to increased control of cervical lymph node metastasis.

For the diagnosis of cervical lymph node metastasis, cervical lymph node assessment involving squamous cell carcinoma of the oral region was used in our department and was reported to be useful[1]. The method of assessment included CT and Ultrasonography (US) imaging evaluations in addition to malignancy based on clinicopathological findings for the primary lesion at the initial examination. Based on the results of the above study, we have created criteria for the treatment of cervical lymph node metastasis which have been applied clinically[2].

Furthermore, since 1985, we have established a systematic treatment in our department. Chemotherapy is ascertained for each patient based on his/her degree of malignancy, and a sequential resection is applied based on the response to chemotherapy as well as the malignancy of his/her primary lesion[2-4]. As a result, reexamination of treatment for advanced cases and cases of high-grade malignancy have become an issue[5]. Since July 1997, we have therefore performed super selective intraarterial infusion of carboplatin (CBDCA) with concurrent radiotherapy (SIACR, hereinafter) in advanced cases and cases of high-grade malignancy. This treatment was performed with the purpose of enhancing the preoperative therapy to improve the treatment result. The main reason for this improvement was believed to the therapeutic effect of SIACR on the primary lesion as well as cervical lymph node metastasis, the latter causing an improvement in the control rate of cervical lymph node metastasis[6].

However, there are few reports on patients diagnosed as metastasis-positive by cervical lymph node metastasis who were then treated by SIACR. In particular, the relative benefits of this therapy

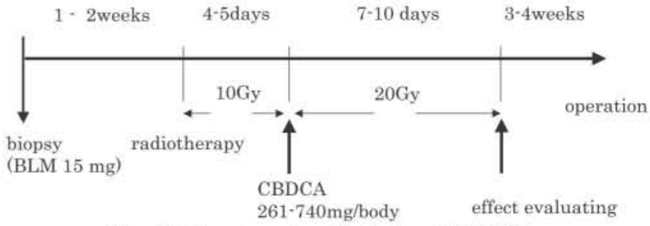

Fig. 1 Treatment schedule of SIACR

and an analysis of cross-modality imaging have not been widely reported.

Here, patients with metastasis-positive cervical lymph nodes were treated with SIACR in our hospital to determine the benefits and effects of chemotherapy for cervical lymph node metastasis.

MATERIALS AND METHODS

Patients

Twenty seven patients with biopsy-proven squamous cell carcinoma of the oral and maxillofacial region underwent SIACR with carboplatin (CBDCA) for cervical lymph node metastasis and neck dissection. All were examined by computed tomography (CT) and ultrasonography (US) before and after SIACR, and metastatic lymph nodes were diagnosed according to a criterion (CT imaging diagnostic criteria: short-axis of 10 mm or more, or presence of rim enhancement and US imaging diagnostic criteria: short-axis of 10 mm or more, clarity of boundary echo, and heterogeneity of internal echo)[1]. The site of primary tumor were in decreasing order of frequency, 7 in the tongue, 5 each of the buccal mucosa and the lower gingiva, 4 each in the floor of the mouth and the oropharynx, and 2 in the upper gingival. Neck dissection was performed after preoperative SIACR at the Department of Oral and Maxillofacial Surgery, Hospital of the University of the Ryukyus, from July 1997 to December 2002. All patients were treated with consent in this hospital based on a schedule of treatment (Fig.1).

Clinical and histological findings for primary site

TNM and stage classification of primary tumor sites were performed and reported according to the International Union Against Cancer (UICC) criteria[7]. The growth pattern of tumors was classified into two types: exophytic and endophytic growth. Biopsy specimens were fixed with 10% formalin and further processed according to

Table 1 Clinical and disease characteristics of patients

Sex:	male: 21	female: 6		
Age:	34～77	(mean age: 62)		
Primary site :	tongue: 7	lower gum: 5	buccal mucosa: 5	
	floor of mouth: 4	oropharynx: 4	upper gum: 2	
T classification:	T1: 1	T2 : 7	T3: 3	T4:16
N classification:	N1: 10	N2a: 2	N2b:11	
	N2c: 3	N3: 1		
Differentiation:	well: 7	moderate: 16	poor: 4	
Mononuclear infiltration:	strong: 3	moderate: 16	weak: 8	
Number of mitotic cell:	few: 8	moderate: 13	many: 6	
Mode of cancer invasion:	type4C: 2	type2: 4	type4D: 5	
	type3: 16			
Grade of malignancy:	moderate: 18	high: 9		

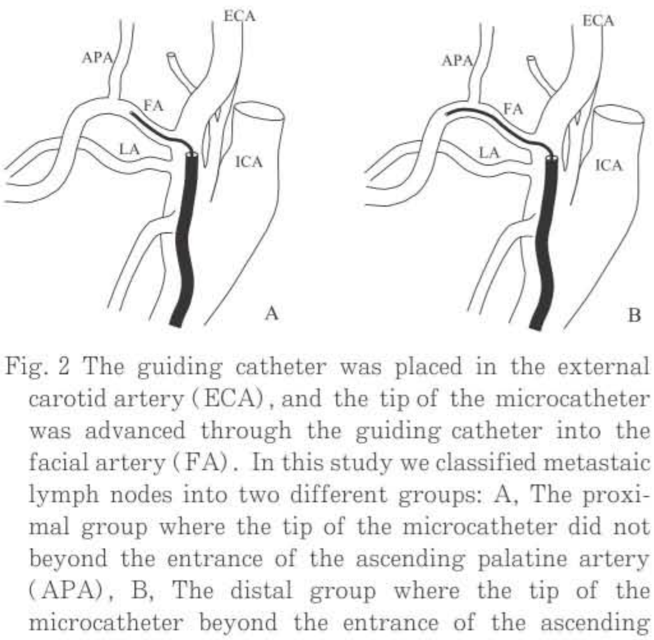

Fig. 2 The guiding catheter was placed in the external carotid artery (ECA), and the tip of the microcatheter was advanced through the guiding catheter into the facial artery (FA). In this study we classified metastaic lymph nodes into two different groups: A, The proximal group where the tip of the microcatheter did not beyond the entrance of the ascending palatine artery (APA), B, The distal group where the tip of the microcatheter beyond the entrance of the ascending palatine artery (APA).

standard methods. After paraffin embedding, 4-μm sections were stained with hematoxylin-eosin. The tumor parenchyma grade of differentiation, degree of mononuclear cell infiltration, number of mitotic cells, mode of cancer invasion and grade of malignancy of primary tumor sites were determined. Clinicopathological malignancy was evaluated by score based on the initial clinical and histological findings (Table 1)[1-3,5,6].

CBDCA selective Intra-arterial Infusion Chemotherapy and Radiotherapy

All catheterizations were performed via a transfemoral approach by the Seldinger technique. The diagnostic angiographic procedure was routinely performed with a standard diagnostic catheter using digital subtraction angiography (DSA). Depending on primary tumor location, a 2.5 Fr microcatheter was placed in the appropriate feeding artery using the coaxial technique. The position of the microcatheter was checked by injection of indigo carmine. All metastatic cervical lymph nodes were also treated with intra-arterial infusion via the facial artery for Level I or proximal external carotid artery. The tip of the microcatheter was advanced as far distally as possible into the facial artery to prevent unnecessary infusion into the mucosal of muscular branches. In this study we classified 17 nodes of the total 22 Level I metastaic lymph nodes (5 nodes that the placement of the tip of the microcatheter can not be judged on DSA images) into two different groups: proximal group where the tip of the microcatheter did not extend beyond the entrance of the ascending palatine artery, and distal group where the tip of the microcatheter did extend beyond the entrance of the ascending palatine artery (Fig. 2). In 9 of 27 patients, computed tomography angiography (CTA) was performed to evaluate the vascularity and extent of the primary tumor and metastatic lymph nodes (Fig. 3).

The dosage of CBDCA was calculated using the formula of Calvert[8].

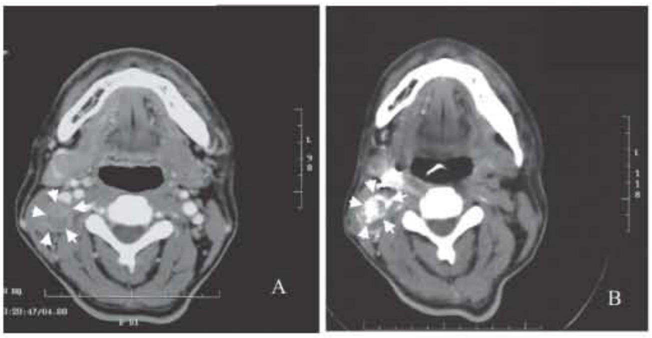

Fig. 3 A, A 55-years-old man with lingual carcinoma (T2N1M0). A metastatic lymph node (arrows) was showed in CT scan image.
B, A CT angiography (CTA) showed enhancement of a metastatic lymph node (arrows)

Histological findings for cervical lymph nodes

Neck dissection was performed within four weeks after SIACR. All surgical tumor specimens were fixed with 10% formalin and processed according to standard methods. All identifiable lymph nodes were submitted for evaluation of lymph node status. Sections were stained with hematoxylin-eosin. All histological analyses were carried out independently by a pathologist. The histological response of nodes to preoperative treatment was categorized according to the histological grading system established by Shimosato et al[9]: Grade 0. No curative effect is accepted in cervical lymph node metastasis. Grade 1. Minimal cellular changes present but a majority of cells appear viable. Grade 2. In addition to characteristic cellular change, tumor structures have been destroyed as a result of disappearance of tumor cells. Grade 2a. Destruction of tumor structures id of mild degree, i.e., "vi able tumor cells" are frequently observed. Grade 2b. Destruction of tumor structures is of severe degree, that is, "viable tumor cells" are few in number. Grade 3. Markedly altered, presumably non-viable tumor cells are present singly or in small clusters and "viable cells" are hardly seen. Grade 4. No tumor cells remain in any sections. For the nodes of grade 4, we used the report of Westra et al. as a reference[10]. We examined the following to verify the disappearance of cancer cells caused by SIACR: presence or absence of fibrotic cells (fibrosis), histiocytic infiltration, and foreign body giant cells.

Ultrasonography (US) and computed tomography (CT)

Ultrasonography was performed using a unit (RT-2800; General Electric Yokogawa Medical Systems, Tokyo, Japan) equipped with a transducer (H type, 7.5 MHz). Long and short axes diameters of lymph nodes, edge definitions, margins, patterns of internal echo, intensities of internal echo, and echogenic hili were carried out with a caliper on ultrasonography.

Patients were scanned using two CT systems (LightSpeed QX/I; General Electric Medical Systems, Milwaukee, Wisconsin USA and X-VIGOR apparatus; Toshiba Medical Inc. Japan). The scanning orientation was parallel to the Frankfort horizontal plane. Scans were performed using a helical technique to acquire 5 mm-thick contiguous sections, and were conducted from the sternum to the base of the skull with intravenously administered contrast material. Pretreatment CT scans were obtained at an average of 2 weeks before beginning SIACR, and post-treatment scans were obtained at an average of 4 weeks after completion of SIACR. CT images were scanned to image files by a scanner (Canoscan 600; Canon Inc. Japan) and documented on print paper using a laser printer (LBP870; Canon Inc. Japan). All scan analyses were carried out independently by one of the authors and two radiologists experienced in CT of the head and neck region. Short-axis diameters of lymph nodes were measured by them without additional clinical information, such as the presence of lymph node metastases, and without histological information.

Statistical procedures

Statistical analyses were carried out with the SPSS (ver 10.0.1, 1999, SPSS Inc. Chicago, USA) using the Man-Whitney U and χ^2 test.

RESULTS

Findings for a total of 38 cervical lymph nodes diagnosed as bearing metastasis before SIACR and reevaluated with CT after treatment were correlated with histological findings. The histological response of the nodes was judged as grade 1 in 2 nodes (5%), grade 2a in 6 nodes (16%), grade 2b in 10 nodes (26%), grade 3 in 6 nodes (16%), and grade 4 in 14 nodes (37%). To simplify the correlation with histological response, histological responses were

Table 2 Clinical and histological findings of Grade Ⅳ lymph nodes

Case	Primary site	Level of metastasis	Histologic findings		
			Fibrosis	Histiocyte	Giant cell
1	Lower gum	Ⅰ	(+)		
2	Tongue	Ⅱ		(+)	
3	Buccal mucosa	Ⅱ	(+)	(+)	
4	Lower gum	Ⅰ	(+)	(+)	
5	Lower gum	Ⅱ	(+)	(+)	
6	Floor/mouth	Ⅰ	(+)	(+)	
7	Tongue	Ⅰ	(+)	(+)	
8	Oropharynx	Ⅱ	(+)	(++)	
9	Floor/mouth	Ⅰ	(++)	(+)	
10	Tongue	Ⅱ	(+)	(++)	(+)
11	Buccal mucosa	Ⅰ	(+)	(+)	(+++)
12	Tongue	Ⅱ	(+)	(+)	(+++)
13	Tongue	Ⅰ	(+++)	(++)	(+++)
14	Tongue	Ⅱ	(+++)	(+++)	(++)

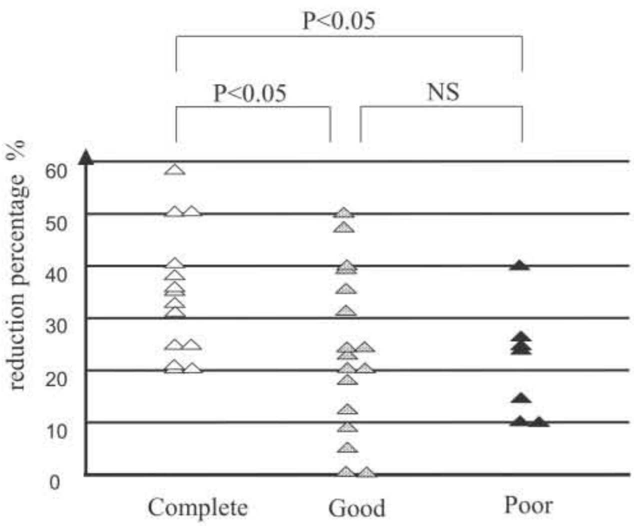

Fig. 4 The relationship between histological response and reduction percentage of short-axis diameters for 38 metastatic lymph nodes. Complete response nodes showed a significant reduction in short-axis diameters compared with good and poor response nodes, using the Mann-Whitney U test.

classified as "poor" for grades 1 and 2a, "good" for grades 2b and 3, "complete" for grade 4. For the " complete" (grade 4) group, the presence or absence of fibrotic cells (fibrosis), histiocytic infiltration, and foreign body giant cells were examined. Cellular changes were observed in all grade 4 nodes. Five (36%) of 14 nodes exhibited all types of cellular change and 12 (86%) nodes exhibited more than two types of cellular changes (Table 2).

The short-axis diameters measured on CT scans ranged from 10 to 42 mm with a mean of 15 mm before SIACR and ranged from 10 to 40 mm with a mean of 11 mm after SIACR. No patient had an increase in lymph node short-axis diameter after treatment. There were 36 (95%) lymph nodes with decreased short-axis diameters, excluding 2 nodes with no change. The percentages of reduction were 0%-58%, with a mean of 26%. The 14 "complete" response lymph nodes were within the range of 20% to 58%. The reduction percentages of 17 "good" response nodes and 7 "poor" response nodes were within the range of 0% to 50% and 10% to 40%, respectively. The correlation between percentage reduction of lymph node short-axis diameter and histological response were 35%±12%, 24%±15%, and 27%±11% for "complete", "good" and "poor", respectively. Nodes with complete response exhibit a significant reduction in short-axis diameter compared with those with good and poor response ($P<0.05$ using the Mann-Whitney U test) (Fig. 4).

The relationship between histological response and placement of the microcatheter tip in Level I lymph nodes is shown in Table 3. In the proximal group, no lymph node exhibited a complete response. Five (63%) and 3 (37%) lymph nodes exhibited a good response and poor response. On the other hand, no lymph node exhibited a poor response in the distal group. Four (44%) and 5 (56%) lymph nodes exhibited complete and good responses, respectively. The difference in proximal and distal

Table 3 Relationship between histological responses and the placement of the tip of the microcatheter in the group of Level I lymph nodes ($P<0.05$)

Histologic response	proximal group n=8(%)	distal group n=9(%)
complete	0	4(44)
good	5(63)	5(56)
poor	3(37)	0

Table 4 The relationship between histological response of lymph nodes after CBDCA SIACR and lymph nodes enhancements evaluated using a CT angiography system

Histological response	Enhancements (+) No. of nodes (%) n=11	Enhancements (−) No. of nodes (%) n=3
complete	5(45)	0
good	6(55)	1(33)
poor	0	2(67)

group according to the histological response was statistically significant ($P<0.05$).

In 9 of 27 patients for whom vascularity and extent of tumor staining were evaluated using CTA. Only 11 lymph nodes of the total 14 nodes that dense enhancements were identified by CTA, the histological response of lymph nodes was good. Among them, 5 (46%) nodes had complete responses and 6 (55%) had good responses; none had a poor response. Three lymph nodes of 14 nodes were not enhanced on CTA images, among them, 2 (67%) had poor responses; one had a good response (Table 4).

DISCUSSION

The presence or absence of cervical lymph node metastasis greatly influences patient prognosis, and metastasis-positive patients have less favorable prognoses than metastasis-negative patients[11]. In particular, the prognosis is very unfavorable for patients with metastasis more distal than level III[12]. However, the majority of cervical lymph node metastases are confined to levels I to II, and most patients have 1-2 metastases[13]. When considering control of cervical lymph node metastasis, measures against such cases are particularly important. In our study, we examined the effects of and factors related to the effect of SIACR in patients with lymph node metastasis of levels I to II, who account for the majority of those with cervical lymph node metastasis.

Accurate diagnosis of cervical lymph node metastasis is extremely important for the determination not only of the most appropriate treatment method but also of therapeutic effect. In recent years, there have been many reports on the improvement of the accuracy of diagnosis of cervical lymph node metastasis with the use of various imaging methods, such as CT, US, and MRI[14,15]. We reported very high diagnostic accuracy with 90% sensitivity, 100% specificity, and 94% accuracy when clinicopathological malignancy scores (12 points or more) were used as diagnostic criteria in addition to the CT imaging diagnostic criteria and US imaging diagnostic criteria[1]. Based on the results of these previous studies and in order to obtain high diagnostic accuracy, here we performed comprehensive assessments of cervical lymph nodes according to our department's diagnostic criteria for lymph node metastasis prior to diagnosis.

1) Application of SIACR to treat cervical lymph node metastasis

In general, SIACR is used for local treatment of a primary lesion. Chemotherapy is unsuccessful in treating lymph node metastasis because it is difficult to transport anticancer drugs to lymph node tissues[16-18]. Watanabe et al. studied the transport of CDDP into cervical lymph node tissues in rats. It becomes evident that a lymphatic transport pathway exists in addition to a blood pathway from the target organ to the cervical tissues. In the group that underwent intra-arterial infusion concentration dynamics of CDDP was used in the cervical tissues on the side administered CDDP[19]. The result provides basic evidence that intra-arterial treatment may be effective for associated lymph nodes. The use of SIACR for cervical lymph node metastasis is thus based on scientific evidence.

2) Effect of SIACR

There are only a few reports indicating the clinical effectiveness of treating cervical lymph node metastasis. Most previous studies used US imaging finding parameters to evaluate clinical effectiveness[20]. However, poor reproducibility of surrounding tissues, and lymph node tissues are a common assessment problem using US imaging. In particular, when lymph nodes are assessed at different times before and after treatment, it is sometimes difficult to accurately identify the nodes that are to be used for comparison. CT shows the anatomical relationships of the surrounding tissues more objectively and also has the advantage of good reproducibility[1]. However, few studies of the clinical effectiveness of intra-arterial infusion chemo-radiotherapy along with examining lymph node metastasis applying CT imaging have been carried out in a large number of patients[21]. Yusa et al. reported the use of US imaging to examine the following changes of the lymph node: short and long axes diameters, edge definitions, margins, patterns of internal echo, intensities of internal echo, echogenic hili, and patterns of blood flow before and after intra-arterial infusion chemo-radiotherapy. They found that only the long and short-axis diameters of lymph nodes in the patients with "complete" response exhibited statistically significant changes[20]. Moreover, up to date, there are no judgment methods and criteria of evaluation relating to the clinical response of a lymph node, and many other researchers have reported the usefulness of CT short-axis diameter values in the assessment of metastatic lymph nodes[22,23]. Therefore, in our study, we decided to use the lymph node CT short-axis diameter values used in a diagnosis of cervical lymph nodes as a criteria of evaluation.

Many researchers assess histological responses according to the histological grading system established by Shimosato et al[9] which evaluates effectiveness based on the quantitative ratio of surviving and dead cancer cells[20,24]. In our study, we used the same system to determine histological responses. Histological response rates were 41% for the "good" response groups (grade 2b and grade 3) and 38% for the "complete" response group (grade 4); the overall histological response rate was 78%, indicating favorable results and similar results as those in other reports[25].

An examination of the relationship between clinical responses and histological responses of metastatic nodes revealed that as histological responses increased, the rate of reduction of lymph nodes tended to increase. Other studies that treated patients with chemoradiotherapy yielded similar results and a similar relationship between clinical effectiveness and histological responses was observed[24].

From the above results, SIACR is suggested to be an effective strategy against cervical lymph node metastasis.

3) Factors related to the efficacy of SIACR

(1) Position of the tip of the microcatheter

It has been said that the skill of an interventional radiologist performing microcatheter insertion affects the therapeutic effect of SIACR. In SIACR, it is important to accurately identify the feeding artery that transports the drug in high concentration to the metastatic lymph node and to reliably insert the microcatheter into the feeding artery with care taken to avoid vascular spasms[26]. These precautions greatly influence the therapeutic effect. In many cases, the glandular branches of the facial artery are the main feeding arteries to level I submandibular lymph nodes. In order to allow the drug at a higher concentration to reach the target lymph node, the tip of the microcatheter needs to be inserted beyond the entrance of the ascending palatine artery to reduce loss of the drug. However, in some cases the tip of the microcatheter cannot be placed distal to the bifurcation of the ascending palatine artery due to conditions such as vascular tortuousness, reduction of vascular diameter, and occurrence of vascular spasm. Therefore, in our study, we examined the relationship between histological responses and positioning of the tip of the microcatheter in level I submandibular lymph node metastasis, which has a comparatively uniform tumor feeding artery. Positions were divided into those proximal to the branching site of the ascending palatine artery, the first branch of the facial artery, and distal to that site. Histological response was greater for patients in whom the tip of the microcatheter was placed distal to the branching site of the ascending palatine artery. It thus appeared that placement of the tip of the microcatheter peripheral to the ascending palatine artery, the first branch of the facial artery, is the preferred position at the time of infusion for level I lymph node metastasis. This result is important in determining the diagnostic criteria for positioning of the microcatheter tip at institutions without CT angiography (CTA) facilities.

(2) Importance of CT angiography (CTA)

There are many branches of feeding arteries to a level II lymph node metastasis. Confirmation of drug transport to a metastatic lymph node cannot be made with a general contrast-enhanced study. CTA has been reported to be required for this[27]. Since 2000, we have used CTA to confirm transport of the contrast medium to the metastatic lymph node, and then administered an anticancer drug. To examine the usefulness of CTA, we compared the histological responses in patients for whom contrast medium was confirmed to have been transported to the metastatic lymph node with other patients. The group with contrast medium transported to the lymph node metastasis showed a far better histological response. This highlights the importance of confirmation of drug transport by CTA in SIACR for lymph node metastasis. In particular, confirmation of drug transport by CTA is considered to be important for metastatic lymph nodes more distal than level II.

4) Future role and issues of SIACR for cervical lymph node metastasis

In general, the first choice for curative treatment for cervical lymph node metastasis is cervical dissection. Radiotherapy and chemotherapy have supportive roles in the present state of medical practice. However, there have recently been cases in which chemoradiotherapy and SIACR have been used for lymph node metastasis[28~30]. Since there are important structures such as the internal carotid arteries and vagus nerves in the cervical region, surgical resection has limits. However, with SIACR, high concentrations of anticancer drugs can act directly on lymph node metastasis. Preoperative antitumor effect on cervical lymph node metastasis is believed to increase the cervical control rate. This is clinically significant and it is important to establish super-selective intra-arterial therapy as a treatment choice for cervical lymph node metastasis.

An important issue for the future has been raised, that of having higher concentrations of anticancer drugs to lymph nodes with multiple feeding arteries. To address this issue, establishment of a reliable method of selecting the appropriate tumor feeding artery is needed. Accurate assessment of drug transport to metastatic lymph nodes is difficult with indigo carmine and arteriography alone. Therefore, there is an urgent need to establish a treatment method using CTA to confirm such drug transport. Other issues that remain to be addressed include the establishment of efficient decision criteria for optimal drug distribution to the primary lesion and cervical lymph node metastasis. Additionally, decision criteria need to be established for optimal drug distribution when there are multiple lymph node metastases at multiple levels.

ACKNOWLEDGMENTS

The authors would like to thank Prof. Sadayuki Murayama and Associate Professor Takafumi Toita, Department of Radiology, University of the Ryukyus for their valuable comments on the manuscript.

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