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Author(s)	Sakashita, Tomohiro; Homma, Akihiro; Oridate, Nobuhiko; Suzuki, Seigo; Hatakeyama, Hiromitsu; Kano, Satoshi; Mizumachi, Takatsugu; Yoshida, Daisuke; Fujima, Noriyuki; Fukuda, Satoshi
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Title:

Platinum concentration in sentinel lymph nodes after preoperative intra-arterial cisplatin chemotherapy targeting primary tongue cancer.

Author names:

Tomohiro Sakashita, Akihiro Homma, Nobuhiko Oridate, Seigo Suzuki, Hiromitsu Hatakeyama, Satoshi Kano, Takatsugu Mizumachi, *Daisuke Yoshida, *Noriyuki Fujima, Satoshi Fukuda.

Department:

Department of Otolaryngology- Head & Neck Surgery, Hokkaido University Graduate School of Medicine. Sapporo, Japan.

*Department of Radiology, Hokkaido University Graduate School of Medicine. Sapporo, Japan.

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Corresponding author: Tomohiro Sakashita

Department of Otolaryngology-Head and Neck Surgery,
Hokkaido University Graduate School of Medicine.

Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

Phone: +81-11-707-3387; Fax: +81-11-717-7566;

E-mail address: t-sakashita@med.hokudai.ac.jp

Key words: intra-arterial chemotherapy, sentinel node, cisplatin, nodal metastasis, preoperative chemotherapy

Running title: Pt concentration in SN after cisplatin arterial infusion.

ABSTRACT

Conclusion. We concluded that intra-arterially injected cisplatin passed via lymph flow into sentinel nodes (SNs) as the platinum concentration in the SNs was higher than that in the non-sentinel nodes (NSNs). It is possible that pre-operative intra-arterial chemotherapy targeting primary cancer also has a therapeutic effect on subclinical metastatic SNs.

Objectives. Intra-arterial chemoradiotherapy has been reported to be effective against not only primary tumors but also nodal metastases. We considered the hypothesis that intra-arterially injected cisplatin passed via lymph flow into regional nodes. This study aimed to investigate intra-arterially injected cisplatin distribution to regional nodes by comparing platinum concentrations in SNs and NSNs.

Method. Five patients with T1-2 N0 tongue cancer were treated with preoperative intra-arterial chemotherapy (cisplatin, 100mg/m²) targeting primary cancer. Partial glossectomy together with SN biopsy and elective neck dissection were performed two weeks after intra-arterial chemotherapy. Platinum concentrations in the lymph nodes were measured using a Zeeman atomic absorption spectrometer.

Results. Thirteen SNs were harvested together with 8 NSNs from the adjacent areas to the SNs. Platinum concentrations were then measured, revealing a significant difference in platinum concentration between the SNs and the NSNs (mean±SD, 0.682±0.246 µg/g vs 0.506±0.274 µg/g; p=0.049).

INTRODUCTION

Intra-arterial chemotherapy and concurrent radiotherapy (RADPLAT) has been reported to be effective for head and neck squamous cell carcinomas (HNSCC) [1-2]. RADPLAT has a high impact on the primary site, and some reports have shown high nodal control rates for RADPLAT as well [3-5]. However, the mechanism which by intra-arterially injected cisplatin is distributed to the regional lymph nodes remains to be clarified. We, therefore, considered the hypothesis that intra-arterially injected cisplatin passed via lymph flow into the regional lymph nodes.

Recently, the concept of sentinel lymph node (SN) was established for head and neck squamous cell carcinomas, particular for oral cancer [6-8]. This study aimed to investigate intra-arterially injected cisplatin distribution to the regional nodes by comparing platinum concentrations in SNs and non-sentinel lymph nodes (NSNs).

MATERIALS AND METHODS

Patients and pre-treatment evaluation. Five patients with tongue cancers were diagnosed clinically as T1-2 N0 and were treated in our institution since 2010. Informed consent for the current clinical study was obtained from all five patients. Clinical staging was determined using computed tomography (CT) scanning and magnetic resonance (MR) imaging, and positron emission tomography (PET) -CT scanning and clinical examination by multiple specialists in head and neck surgery and radiology and dentistry. Tumors were classified according to the American Joint Committee on Cancer (AJCC) staging system (7th edition, 2010). Four patients were classified as T2N0, and the remaining patient (case 1) was classified as T1N0. (Table 1.)

Approval for this study was obtained from the institutional review board at Hokkaido University. Completion of the survey was considered as implied consent for participation.

Preoperative chemotherapy. Intra-arterial cisplatin chemotherapy was performed for all five patients, using Seldinger's technique. Cisplatin was administered at a dose of 100mg/m², and was injected rapidly (median 0.4ml/sec; mean 0.5ml/sec) to the lingual artery on the primary tumor involved side. Sodium thiosulfate (24g/body) was simultaneously administered intravenously for neutralization. We performed partial glossectomy together with SN biopsy and elective neck dissection two weeks after the intra-arterial cisplatin chemotherapy.

Sentinel node scintigraphy. On the day before surgery day, we injected ^{99m}Tc -labeled phytate 75mBq (1ml) to the peri-primary tumor site and SN scintigraphy was performed one hour after injection. Five surfaces (posterior to anterior and two transverse lines and two oblique lines) were scanned using a gamma camera. The scanning one surface took five minutes for the detection of a radioactive points and imaging.

Surgical treatment. Within 18 hours after the ^{99m}Tc -labeled phytate injection, we performed partial glossectomy. We performed SN biopsy and elective neck dissection (level I, II, III on disease side) following glossectomy. A C-Trak collimated gamma probe (model CW3000; Carewise Medical Corp., Morgan Hill, California, United states) was used for detecting radioactivity and measuring the over-threshold counts for ten seconds. Radioactive nodes with counts that were ten times higher than the background counts recorded as SNs. SNs were analyzed pathologically at 2mm intervals and sliced into 4 μm thick sections, and diagnosed using cytokeratin immunochemical staining (AE1/AE3). Histopathological degenerative change in metastatic lymph nodes after pre-operative chemotherapy was evaluated using histological criteria in previous report [9]. We harvested one NSN as a control from one area adjacent to the harvested SN.

Measurement of platinum concentration. We measured platinum concentrations in the primary tumors, SNs, and NSNs using a polarized Zeeman atomic absorption spectrometer (model: 170-70; Hitachi ,Ltd., Tokyo, Japan). Primary tumor tissues and node tissues were cut into 1mm block. These specimens were digested at 176°F for five hours using nitric acid and were chelated with sodium diethyldithiocarbamate. After chloroform extraction, these specimens were available for atomic absorption spectrometer.

Statistics. A mixed effect model was applied for comparison of the platinum concentrations in SNs and NSNs, an unpaired t-test was applied when the platinum concentrations of two unpaired groups were compared.

RESULTS

Treatment outcomes. All five patients underwent preoperative intra-arterial cisplatin infusion to the lingual artery on the tumor involved side. In cases 1 to 4, cisplatin was administered successfully at a dose of $100\text{mg}/\text{m}^2$. In case 5, the cisplatin dose was $80\text{mg}/\text{m}^2$ because of the patient's advanced age (81 years). Partial glossectomy together

with SN biopsy and elective neck dissections were performed successfully two weeks after pre-operative intra-arterial chemotherapy in all 5 cases. There were no adverse events after preoperative intra-arterial chemotherapy and after surgical treatments in all 5 cases. Multiple metastatic SNs were diagnosed pathologically in case 2. We performed postoperative radiation therapy (60Gy/30fr) with concomitant weekly cisplatin (40mg/m²) chemotherapy for case 2.

Sentinel node detection and pathological findings. We detected and harvested 13 SNs on the primary tumor involved side, using gamma camera and gamma probe. We also harvested 8 NSNs from the areas adjacent to the harvested SNs. No SNs were detected on the contralateral side in any of five cases. Nodal metastases were observed pathologically in 7 of the 13 SNs. However, there were no metastases in the 8 NSNs or in any of the other lymph nodes included in the neck dissection specimens.

In 3 of 7 metastatic SNs, degenerative changes (e.g. swelling of tumor cell, cytolysis, and partial necrosis) were observed histopathologically. However, viable tumor cells and tumor structures remained. In remaining 4 metastatic SNs, tumor nests were very small and histopathological degenerative changes were hardly seen.

Platinum concentrations. Platinum concentrations were measured, revealing a significant difference in platinum concentration between the primary site and lymph node (mean±SD, 1.978±0.807 µg/g vs 0.615±0.265 µg/g; p<0.001). Table 2 shows results for platinum concentration.

The platinum concentrations in the SNs and NSNs were 0.682±0.246 µg/g, and 0.506±0.274 µg/g, respectively. There was a significant difference between the platinum concentration in the SNs and that in the NSNs (p=0.049, Figure 1).

Platinum concentrations in the metastatic SNs (n=7) and non-metastatic SNs (n=6) were 0.645±0.245 µg/g, and 0.724±0.263 µg/g, respectively. There was no significant difference in platinum concentration between metastatic SNs and non-metastatic SNs (p=0.293).

Clinical outcomes. All five patients are still alive without disease. There has been no primary site or regional recurrences in any of the five cases. The median of observation period was 9 months (range 7 to 19 months, mean 12.2 months).

DISCUSSION

The presence of nodal metastasis in oral cancer is one of the most important

prognostic factors and is crucial in making decisions regarding postoperative radiation treatment and follow up. Even in patients with no clinical evidence of lymph node metastasis, there is a high incidence of occult metastasis, which ranges from 10 to 50 % depending on the primary tumor characteristics including tumor subsite, T stage and depth of invasion [10-14]. Additional treatment is not always successful in cases where subclinical nodal metastasis emerges clinically after initial treatment. Therefore, early detection of subclinical nodal metastasis and treatment for subclinical nodal metastasis are important and are considered to contribute to the clinical outcomes.

It is considered that deep invasion of the primary tumor is an important prognostic factor for nodal metastasis and recurrence. A depth of invasion of over 4 or 5mm has been reported to be a risk factor [15-16]. The depth of invasion of the primary tumor in all five cases in our study was greater than 8mm. Although all five of our cases were clinically diagnosed as N0, metastases in the SNs were observed pathologically in all five cases. We therefore reconfirmed that deep of invasion of the primary tumor was an important risk factor for subclinical nodal metastasis.

SN biopsy is considered a useful approach for the detection of subclinical nodal metastasis in patients diagnosed clinically as N0, and the efficacy of SN biopsy was reported and established for patients with oral cancer [6-8].

The application of SN biopsy after intra-arterial chemotherapy was reported by Kovács et.al. [17], who concluded that lymphatic drainage was not significantly altered after intra-arterial chemotherapy targeting the primary tumor. SN biopsy following intra-arterial chemotherapy was, therefore, considered feasible.

Taking the above factors into consideration, preoperative intra-arterial chemotherapy for patients with deeply invasive primary tumors might be expected to be an effective treatment for not only the primary tumor but also subclinical nodal metastasis. Therefore, we investigated preoperative intra-arterial chemotherapy for patients with T1-2 N0 tongue cancers treated in our institute since 2010.

It was reported that intra-arterial cisplatin chemotherapy with concurrent radiotherapy is effective against primary tumors [1-2]. Some reports have also proven the therapeutic efficacy of RADPLAT for neck disease. The nodal control rate of RADPLAT with or without salvage neck dissection was reported to be 87.1- 91% [3-5]. Robbins et al. reviewed 240 patients with HNSCC and nodal metastasis of which 84 underwent salvage neck dissection. On pathological examination of the neck dissection

specimens, 50 patients (60%) were found to have no residual disease. From these reports, RADPLAT can be considered to be an effective treatment for not only primary tumors but also nodal metastases. We, therefore, considered the hypothesis that cisplatin injected into primary tumor by an intra-arterial approach passes via lymph flow into the regional lymph nodes.

Our findings of a higher platinum concentration in SNs than in NSNs support this hypothesis. In addition, histopathological degenerative changes were observed in 3 of 7 metastatic SNs in our study. Based on histopathological grading system by the previous report, these histopathological changes were evaluated as Grade I which indicates initial anti-tumor effect and remaining tumor structures [9, 18]. It is also possible that intra-arterial cisplatin chemotherapy targeting the primary tumor has a therapeutic effect on subclinical metastatic SNs. However, the results of our current study do not provide any evidence of clinical benefit. For revealing clinical benefit of pre-operative intra-arterial chemotherapy, we need further studies.

It was reported that completely occupied metastatic nodes has no accumulation of tracer [19]. When the ratio of metastatic area in the lymph node was more than 90%, it was thought that the tracer could not flow into that lymph node. Therefore, it was considered that intra-arterially injected cisplatin could not reach completely occupied metastatic SNs. The therapeutic efficacy of preoperative intra-arterial chemotherapy for completely occupied metastatic SNs has, therefore, not yet been clarified.

CONCLUSION

We found that the platinum concentration in sentinel nodes was higher than that in non-sentinel nodes after preoperative intra-arterial cisplatin chemotherapy targeting the primary tumor. It is speculated that the intra-arterially injected cisplatin passes via lymph flow into the sentinel nodes. It is also possible that intra-arterial chemotherapy targeting the primary tumor has a therapeutic effect on subclinical metastatic SNs. The strategy of combined preoperative intra-arterial chemotherapy and sentinel node biopsy could, therefore, afford clinical benefits to patients with subclinical metastatic nodes.

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FIGURE LEGENDS

Figure 1. Data plots of platinum concentrations

Abbreviation: SNs, sentinel lymph nodes; NSNs, non-sentinel lymph nodes

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Author names:

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Corresponding author: Tomohiro Sakashita

Reprint request:

Department of Otolaryngology-Head and Neck Surgery,

Hokkaido University Graduate School of Medicine.

Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan

Phone: +81-11-707-3387; Fax: +81-11-717-7566;

E-mail address: t-sakashita@med.hokudai.ac.jp

Table 1. Patient Characteristics and number of Sentinel nodes

Case	Age	Sex	Primary site	TN stage	Size(mm)	Depth	Cisplatin dose	Number of SNs
1	61	M	tongue	T1N0	12 × 12	8mm	100mg/m ²	3
2	35	M	tongue	T2N0	20 × 10	10mm	100mg/m ²	4
3	62	F	tongue	T2N0	22 × 15	9mm	100mg/m ²	4
4	59	M	tongue	T2N0	28 × 14	9mm	100mg/m ²	1
5	81	F	tongue	T2N0	22 × 15	10mm	80mg/m ²	1

Table 2. Summary for Platinum concentrations

Case	Sentinel nodes			Non Sentinel nodes			Primary tumor
	Region	Platinum Concentration($\mu\text{g/g}$)	Metastasis	Region	Platinum Concentration($\mu\text{g/g}$)	Metastasis	Platinum Concentration($\mu\text{g/g}$)
1	lb	0.682	-	lb	0.422	-	2.650
		0.376	+				
	IIa	0.794	-	IIa	0.455	-	
2	lb	0.350	+	lb	0.07	-	1.03
	IIa	0.370	-	IIa	0.57	-	
		0.620	+				
		0.560	+				
3	lb	0.830	+	lb	0.47	-	1.18
	IIa	1.150	-	IIa	0.53	-	
		0.790	-				
		0.560	-				
4	IIa	1.03	+	IIa	1.07	-	2.37
5	IIa	0.75	+	IIa	0.46	-	2.66
mean \pm SD		0.682 \pm 0.246		0.506 \pm 0.274			1.978 \pm 0.807

Abbreviation: SD, Standard deviation

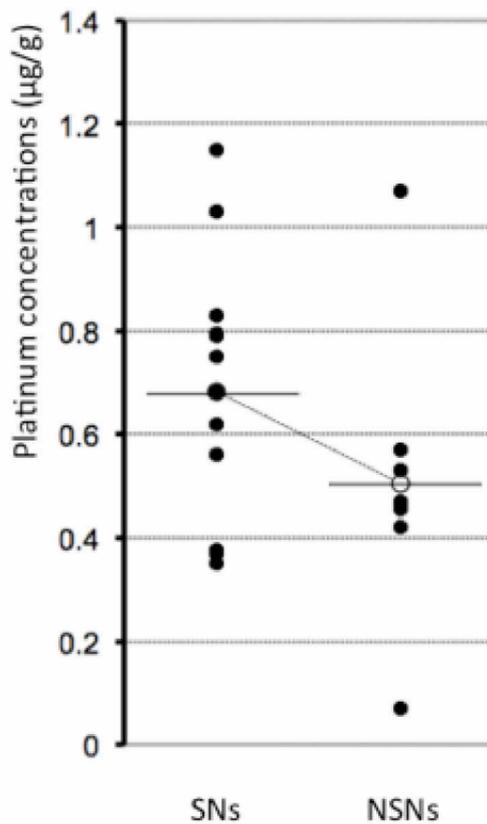


Figure1. Data plots of platinum concentrations

Abbreviation: SN, Sentinel node; NSN, non-sentinel node