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Pilot Study on the Therapeutic Effects of Cisplatin and Docetaxel Superselective Intra-Arterial Infusion and Systemic 5-Fluorouracil Combination Chemotherapy for Stage II Squamous Cell Carcinoma of the Tongue with Greater than 4 mm Depth of Invasion

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ABSTRACT

This study aimed to investigate the effects of superselective intra-arterial infusion of cisplatin and docetaxel and systemically administered 5-fluorouracil combination chemotherapy (i.e., TPF chemotherapy) in patients with stage II squamous cell carcinoma of the tongue with greater than 4 mm depth of invasion (DOI). Eight patients diagnosed with stage II squamous cell carcinoma of the tongue with DOI >4 mm between December 2007 and July 2017 who underwent TPF chemotherapy at Nihon University Hospital at Matsudo were examined retrospectively. Six of the eight patients were managed under wait-and-see policy after chemotherapy and two patients underwent surgery for the primary lesion after chemotherapy. The disease-specific survival (DFS) and recurrence-free survival (RFS) rates of the six patients managed under the wait-and-see policy were compared using the Kaplan–Meier method, and delayed lymph node metastasis was monitored. Both the response and complete response rates were 100% in all patients. The median follow-up period of the six patients was 2915 days. The 5-year DFS and RFS (organ-preserving) rates were 83.3%. The median follow-up period for the two patients who underwent surgery was 2614 days, and primary lesion recurrence was not observed. Delayed metastasis to the cervical lymph nodes was not observed in any of the eight patients. No severe adverse events related to chemotherapy were noted. This study demonstrated the high therapeutic potential of the TPF chemotherapy for stage II squamous cell carcinoma of the tongue with DOI >4 mm.

Key words: Tongue squamous cell carcinoma, Depth of invasion, Cervical lymph node metastasis, Superselective intra-arterial chemotherapy, TPF chemotherapy

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INTRODUCTION

Surgery is considered the standard therapy for stage I (T1N0M0) and II (T2N0M0) tongue cancer [1]. However, many studies report the poor prognosis of patients with squamous cell carcinoma of the tongue with a depth of invasion (DOI) >4 mm, regardless of the cancer stage [2–5]. Therefore, even early-stage cases with DOI >4 mm require aggressive treatment, such as multimodal therapy [2–6]. Combined chemotherapy consisting of a superselective intra-arterial infusion of cisplatin (CDDP) and docetaxel (DTX) and systemically administered fluorouracil (5-FU) (i.e., TPF chemotherapy) has been administered at the Nihon University Hospital at Matsudo as induction chemotherapy to prevent the recurrence of the primary lesion in patients with stage II squamous cell carcinomas of the tongue with DOI >4 mm. Furthermore, we adopted a wait-and-see policy for patients who achieved a complete response (CR) after induction chemotherapy as per clinical and imaging findings, strongly desired to preserve their tongue

and refused surgery, provided a rigorous follow-up is conducted.

This retrospective pilot study aimed to investigate the effects of TPF chemotherapy in patients with stage II squamous cell carcinomas of the tongue with DOI >4 mm.

SUBJECTS AND METHODS

The subjects were eight patients who were diagnosed with stage II (T2N0M0) squamous cell carcinoma of the tongue with DOI >4 mm between December 2007 and September 2017 at the Department of Oral Surgery, Nihon University Hospital at Matsudo and underwent TPF chemotherapy (Table 1). Cancer staging was performed according to the Union for International Cancer Control (UICC) classification [7] and confirmed via contrast-enhanced magnetic resonance imaging (MRI). This study was an open study; the Ethics Committee of Nihon University School of Dentistry at Matsudo approved this study to be conducted by posting an information disclosure document on the website of Nihon University School of Dentistry at Matsudo instead of individual consent forms. This study was approved by the Ethics Review Board of Nihon University School of Dentistry at Matsudo (approval no.: EC 20-012).

CDDP + DTX Superselective intra-arterial chemotherapy was administered after inserting a micro catheter into the radial artery using the Seldinger method to identify the tumor-feeding artery. Digital subtraction angiography was performed, and indocyanine green was used to stain the tissues for identifying the tumor-feeding arteries (Figure 1A and 1B). After identifying the tumor-feeding arteries, sodium thiosulfate (STS) was administered via the central venous catheter to neutralize CDDP. After initiating STS administration, antineoplastic agents, DTX at 20–30 mg/m2 and CDDP at 100–150 mg/m2, were administered to the tumor-feeding arteries super selectively. Next, 5-FU (500–750 mg/m2/day) was systemically administered for 3 days starting from the day after administering the Superselective intraarterial chemotherapy. Two to four cycles of TPF chemotherapy were administered at 3- to 4-week intervals.

Antitumor effects were evaluated using clinical, imaging (computed tomography, MRI, positron emission tomography), and histopathological findings and graded using the revised Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1) [8]. Adverse events associated with chemotherapy were assessed using the Common Terminology Criteria for Adverse Events Version 4.0 [9]. The prognosis was analyzed separately for the six patients who were managed under the wait-and-see policy after chemotherapy and two patients who underwent surgery for the primary lesion after chemotherapy. Statistical analysis was performed using the Kaplan–Meier method to compare the disease-specific survival (DSS) and recurrence-free survival (RFS) rates of the six wait-and-see patients. The occurrence of delayed cervical lymph node metastasis was investigated in all patients.

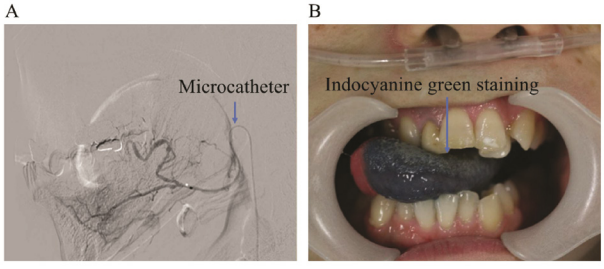

Figure 1: Representative case for the identification of the tumor-feeding artery. (A) Identification of the tumor-feeding artery (lingual artery) via digital subtraction angiography. (B) Staining of the tumor via intra-arterial infusion of indocyanine green.

RESULTS

Patient age and sex

The subjects were of age 27–75 years (median, 57 years) and consisted of seven men and one woman (Tables 1 and Table 2).

Antitumor effects and adverse events

Antitumor effects

After the completion of chemotherapy, antitumor effects were confirmed relatively early in all patients (Figure 2). A reduction in tumor size was observed on imaging (Figure 3). The response and CR rates were both 100% for all patients (Table 2).

Adverse events

The main adverse events were leukopenia, anemia, alopecia, oral mucositis, dysphagia, and nausea/vomiting. Besides grade IV alopecia, all adverse events found were of grade I. No serious adverse events were observed (Table 3).

Post chemotherapy treatment

Two patients underwent surgery for the primary lesion after chemotherapy as initially planned, and the remaining six patients were followed up under the wait-

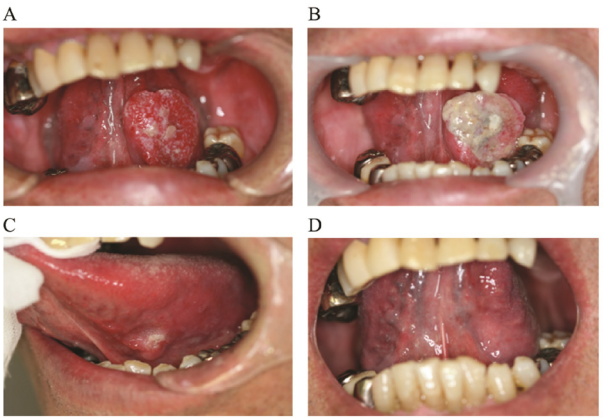

Figure 2: Representative case treated with superselective intra-arterial infusion of cisplatin and docetaxel and systematically administered 5-fluorouracil. (A) Pretreatment tumor condition. Significant reduction of the tumor size by chemotherapy (B) 48 h later, (C) 30 days after completion of one cycle, and (D) 60 days after completion of four cycles.

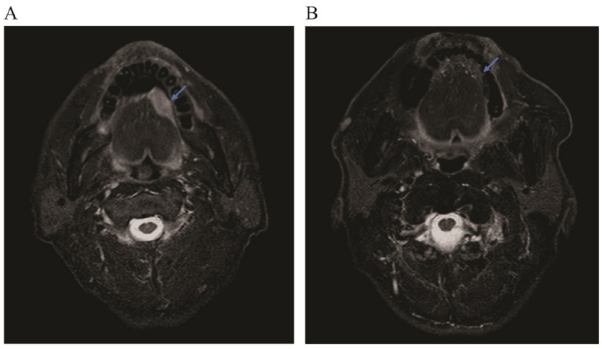

Figure 3: Effects of chemotherapy evaluated by magnetic resonance imaging (short tau inversion recovery image). (A) Tumor appearance before chemotherapy (arrow). (B) Disappearance of the tumor 60 days after the completion of chemotherapy (arrow).

and-see policy because they refused to undergo surgery (Table 1).

Prognosis

The follow-up period of the six patients who were managed under the wait-and-see policy ranged from 572 to 4334 days (median, 2915 days). Recurrence of the primary lesion occurred in one patient (Table 1). The 5-year DSS and RFS (organ-preserving) rates were both 83.3% (Figures 4 and 5). The follow-up periods of the two patients who underwent surgery after chemotherapy were 3745 and 1482 days (median, 2614 days), respectively, and primary lesion recurrence was not observed (Table 1). Furthermore, delayed cervical lymph node metastasis was not observed in any patient (Tables 1 and 2).

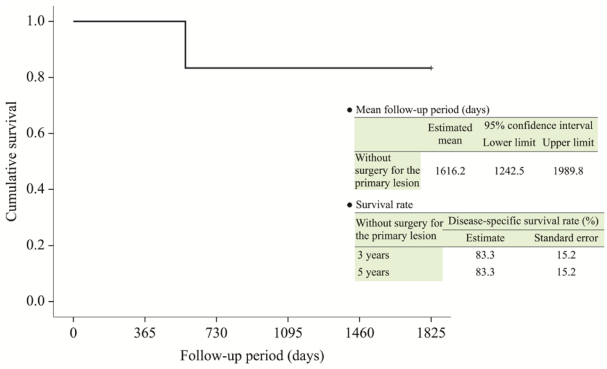

Figure 4: Kaplan–Meier curve for 5-year disease-specific survival: Patients not undergoing surgery for the primary lesion (wait-and-see policy) for up to 5 years.

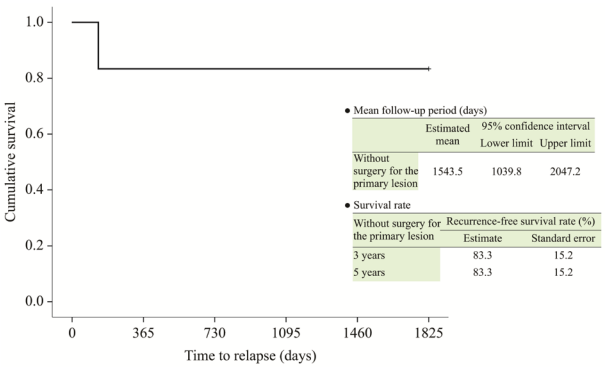

Figure 5: Kaplan–Meier curve for 5-year recurrence-free survival: Patients not undergoing surgery for the primary lesion (wait-and-see policy) for up to 5 years.

Table 1: Characteristics of the patients with squamous cell epithelial cancer of the tongue who underwent treatment with superselective intra-arterial infusion of cisplatin and docetaxel and systemically administered 5-fluorouracil.

	Gender	Age	Maximum diameter of the tumor (mm)	Tumor depth (mm)	Antitumor effects	Surgery for the primary lesion	Recurrence of the primary lesion	Delayed cervical lymph node metastasis	Follow-up period (days)
1	Female	39	22	7.5	CR	Yes	No	No	1482
2	Male	50	25	9	CR	No	No	No	2604
3	Male	75	22	6	CR	No	No	No	2707
4	Male	61	29	5	CR	No	No	No	3122
5	Male	27	21	9	CR	No	No	No	3587
6	Male	74	23	9	CR	No	No	No	4334
7	Male	53	26	6	CR	Yes	No	No	3745
8	Male	66	29	9	CR	No	Yes	No	572

CR: Complete response

Table 2: Summary of the post chemotherapy follow-up.

Case Summary	Median age	Response rate (%)	Complete response rate (%)	Delayed cervical lymph node metastasis rate (%)	Median follow-up period (days)
All cases	57	100	100	0	2915
Wait-and-see cases	64	100	100	0	2915
Surgery for the primary tumor	46	100	100	0	2614

Table 3: Chemotherapy-associated adverse events graded according to the common terminology criteria for adverse events.

Adverse events	Grade			
	1	2	3	4
Leukopenia	1	0	0	0
Anemia	1	0	0	0
Alopecia	0	0	0	8
Dysphagia	3	0	0	0
Oral mucositis	3	0	0	0
Nausea/vomiting	3	0	0	0

DISCUSSION

The prognosis of patients with squamous cell carcinoma of the tongue differs according to the tumor DOI. The prognosis is poor even in stage I or II carcinomas of the tongue if DOI is greater than 4 mm, which also increases the risk of delayed metastasis to the cervical lymph nodes [2–4]. The National Comprehensive Cancer Network Guidelines also recommend cervical lymph node dissection for tumors with DOI >4 mm [5]. Therefore, comprehensive treatment is deemed necessary for patients with squamous cell carcinomas of the tongue with DOI >4 mm [4].

Considering the above information, we have introduced TPF chemotherapy for stage II squamous cell carcinoma of the tongue when DOI >4 mm as part of the comprehensive treatment. CDDP + 5-FU combined chemotherapy (i.e., PF chemotherapy) is considered the gold standard chemotherapy regimen for head and neck squamous cell carcinomas [10]; however, higher response rates have been reported with DTX + CDDP [11,12] and, more recently, with TPF chemotherapy [13]. Concomitant use of CDDP and DTX enhances the intratumoral accumulation of CDDP, thereby enhancing its effects [14]. The combination of DTX and CDDP has been reported to be particularly effective when administered via intra-arterial infusion, resulting in higher CR rates for the primary lesion [15].

Adverse events are a disadvantage of chemotherapy. However, in superselective intra-arterial chemotherapy, STS is administered via the superior vena cava so that CDDP can be neutralized before venous return, thereby minimizing the adverse events caused by CDDP and allowing the administration of higher doses of CDDP [16,17].

We attributed the absence of serious adverse events in this study to the benefits of CDDP neutralization achieved through superselective intra-arterial infusion. Superselective intra-arterial chemotherapy may be administered as chemotherapy with or without radiotherapy [17-19]. Almost all facilities treat superselective intra-arterial chemotherapy alone in resectable cases as preoperative adjuvant chemotherapy [16,19]. However, superselective intra-arterial chemo radiation therapy is frequently used as a radical treatment [17,18]. Our department has been administering TPF chemotherapy as induction chemotherapy, which has resulted in long-term RFS among patients who achieved CR and declined surgery. The 5-year DFS after surgery for primary stage I and II tongue carcinoma is 70%–79.6% [20,21]. In this study, the 5-year RFS of patients who were managed under the wait-and-see policy was 83.3%, suggesting that TPF chemotherapy enabled organ preservation.

Occult cervical lymph node metastasis is reported to occur in 25%–50% of patients with stage II tongue carcinoma [22-25]. However, in this study, delayed cervical lymph node metastasis was not observed in any patient, suggesting that TPF chemotherapy effectively prevents cervical lymph node metastasis. Moreover, this effect was attributed to the superselective intra-arterial infusion of CDDP and DTX, which diverts treatment from the lymphatic flow to the sentinel lymph nodes to prevent occult cervical lymph node metastasis.

Over 90% of oral cancers are squamous cell carcinomas, and approximately 50%–60% of them are carcinomas of the tongue [1,21]. Controlling the primary lesion and cervical lymph node metastasis is key to improving the survival rate. Tongue cancers are mainly treated surgically. However, surgery for patients with stage II tongue cancer with DOI >4 mm can involve en bloc resection in glossectomy using the pull-through method and neck dissection, which can result in postoperative functional impairments. However, the outcomes of this study demonstrate the potential of TPF chemotherapy for use as a radical therapeutic option for stage II squamous cell carcinoma of the tongue with DOI >4 mm with the intent of preserving the tongue and preventing delayed cervical lymph node metastasis.

This study demonstrates the safety and efficacy of TPF chemotherapy in treating patients with stage II squamous cell carcinoma of the tongue with DOI >4 mm and providing good prognosis. However, this is a pilot study that included a small sample size; therefore, future studies involving a larger sample size are needed.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest associated with this manuscript.

REFERENCES

1. Omura K. Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol 2014; 19:423-430.
2. Asakage T, Yokose T, Mukai K, et al. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. Cancer: Interdiscip Int J Am Cancer Society 1998; 82:1443-1448.
3. Huang SH, Hwang D, Lockwood G, et al. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. Cancer: Interdiscip Int J Am Cancer Soc 2009; 115:1489-1497.
4. Almangush A, Bello IO, Keski–Säntti H, et al. Depth of invasion, tumor budding, and worst pattern of invasion: Prognostic indicators in early-stage oral tongue cancer. Head Neck 2014; 36:811-818.

5. Terada H, Sasaki E, Suzuki H, et al. An examination of the cutoff value of the depth of invasion for prophylactic neck dissection in stage I/II tongue cancer. Acta Otolaryngol 2020; 140:422-426.
6. Mann J, Julie D, Mahase SS, et al. Elective neck dissection, but not adjuvant radiation therapy, improves survival in stage I and II oral tongue cancer with depth of invasion >4 mm. Cureus 2019; 11.
7. Mercante G, Gaino F, Giannitto C, et al. Discrepancies between UICC and AJCC TNM classifications for oral cavity tumors in the 8th editions and following versions. Eur Arch Otorhinolaryngol 2022; 279:527-531.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.
9. Miller TP, Fisher BT, Getz KD, et al. Unintended consequences of evolution of the common terminology criteria for adverse events. Pediatr Blood Cancer 2019; 66:e27747.
10. Kish J, Drelichman A, Jacobs J, et al. Clinical trial of cisplatin and 5-FU infusion as initial treatment for advanced squamous cell carcinoma of the head and neck. Cancer Treat Rep 1982; 66:471-474.
11. Glisson BS, Murphy BA, Frenette G, et al. Phase II trial of docetaxel and cisplatin combination chemotherapy in patients with squamous cell carcinoma of the head and neck. J Clin Oncol 2002; 20:1593-1599.
12. Schöffski P, Catimel G, Planting AS, et al. Docetaxel and cisplatin: An active regimen in patients with locally advanced, recurrent or metastatic squamous cell carcinoma of the head and neck: results of a phase II study of the EORTC early clinical studies group. Ann Oncol 1999; 10:119-22.
13. Vermorken JB, Remenar E, Van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New Eng J Med 2007; 357:1695-1704.
14. Maeda S, Sugiura T, Saikawa Y, et al. Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. Cancer Sci 2004; 95:679-684.
15. Furusaka T. Superselective intra-arterial infusion therapy with docetaxel, cisplatin and 5-fluorouracil for head and neck cancer--for tongue cancer patients in comparison patients with other therapies. Cancer Chemother 2006; 33:1241-1246.
16. Kovács AF, Eberlein K, Hülsmann T. Organ preservation treatment using TPF—a pilot study in patients with advanced primary and recurrent cancer of the oral cavity and the maxillary sinus. Oral Maxillofac Surg 2009; 13:87-93.
17. Robbins KT, Storniolo AM, Kerber C, et al. Rapid superselective high-dose cisplatin infusion for advanced head and neck malignancies. Head Neck 1992; 14:364-371.
18. Homma A, Furuta Y, Suzuki F, et al. Rapid superselective high-dose cisplatin infusion with concomitant radiotherapy for advanced head and neck cancer. Head Neck 2005; 27:65-71.
19. Benazzo M, Caracciolo G, Zappoli F, et al. Induction chemotherapy by superselective intra-arterial high-dose carboplatin infusion for head and neck cancer. Eur Arch Otorhinolaryngol 2000; 257:279-282.
20. Iyer NG, Kim L, Nixon IJ, et al. Outcome of patients with early T1 and T2 squamous cell carcinoma of the base of tongue managed by conventional surgery with adjuvant postoperative radiation. Head Neck 2013; 35:999-1006.
21. Zanoni DK, Montero PH, Migliacci JC, et al. Survival outcomes after treatment of cancer of the oral cavity (1985–2015). Oral Oncol 2019; 90:115-121.
22. Kligerman J, Lima RA, Soares JR, et al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg 1994; 168:391-394.
23. Kaya S, Yilmaz T, Gürsel B, et al. The value of elective neck dissection in treatment of cancer of the tongue. Am J Otolaryngol 2001; 22:59-64.
24. Sparano A, Weinstein G, Chalian A, et al. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otorhinolaryngol Head Neck Surg 2004; 131:472-476.
25. Minamiyama S, Mitsudo K, Hayashi Y, et al. Retrograde superselective intra-arterial chemotherapy and daily concurrent radiotherapy for T2-4N0 tongue cancer: Control of occult neck metastasis. Oral Surg Oral Med Oral Pathol Oral Radiol 2017; 124:16-23.