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ORIGINAL ARTICLE

Can Neoadjuvant Chemotherapy before Definitive Surgery Improve Outcome in Operable Stage IVA Oral Cavity Cancers?

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ABSTRACT

Introduction: *To report the outcome for patients with stage IVA oral cavity (OC) cancer treated by docetaxel-cisplatin–5-fluorouracil (TPF) neoadjuvant chemotherapy (NC) and surgery.*

Methods: *This retrospective cohort study involved 69 consecutive patients with squamous cell carcinoma (SCC) of the OC managed from April 2012 to April 2015. Eleven stage IVA patients were treated by TPF NC before surgery following tumour board assessment. Another 11 stage IVA patients from the same cohort who received upfront surgery and adjuvant treatment were identified as controls.*

Results: *TPF NC was given to four (36.4%) patients with a marginally resectable tumour and seven (63.6%) to prevent rapid clinical progression while awaiting definitive surgery. The median age at treatment was 55 (range, 32-65) years. A median of three (range, 3-4) cycles of NC were given. NC was well tolerated; grade 3 or 4 neutropenia or anaemia were observed in one (9.1%) patient each. Clinical complete response (CR), partial response, stable disease and progressive disease were observed in one (9.1%), five (45.4%), three (27.3%) and two (18.2%) patients, respectively. Complete (R0) resection was achieved in 10 (90.9%) patients. One (9.1%) patient had pathological CR. Median follow-up period was 49.5 months. Overall survival was significantly improved with NC (hazard ratio 0.24, median survival not reached [NR] vs. 12 months, p = 0.022). Distant relapse-free survival was also significantly improved with NC (hazard ratio 0.24, NR vs. 9.5 months, p = 0.024). Locoregional control rates were not significantly different (66% with NC vs. 53% without NC, p = 0.191).*

Conclusion: *The outcomes of our small cohort suggested that TPF NC given before surgery could improve overall and distant relapse-free survival in patients with stage IVA OC SCC.*

Key Words: *Combined modality therapy; Induction chemotherapy; Mouth neoplasms; Taxoids*

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中文摘要

誘導化療對IVA期口腔癌的治療成效

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引言：匯報於IVA期口腔癌患者使用多西紫杉醇－順鉑－5-FU作為誘導化療之療效。

方法：本研究包括連續69位患口腔鱗癌，並在2012年4月至2015年4月接受治療的患者。11名IVA期口腔癌患者在多學科會診評估後接受誘導化療和手術。我們也回顧同一群體另外11名只接受手術和後續治療的IVA期患者作為對照。

結果：在使用誘導化療的11名患者中，其中4名（36.4%）因病情較嚴重不能即時切除，另外7名（63.6%）希望透過誘導化療在等候手術期間減慢病情。接受誘導化療的患者的年齡介乎32至65歲，中位數為55歲。每位患者約接受3至4週期的化療。誘導化療一般能為患者接受，出現3至4級中性白血球過低或嚴重貧血的機會率各為9.1%。接受誘導化療後，10名（90.9%）患者的腫瘤能被手術完全切除。手術樣本病理化驗顯示，1名（9.1%）患者的腫瘤被完全緩解、5名（45.4%）有改善、3名（27.3%）病情穩定以及2名（18.2%）病情惡化。患者中位隨訪時間為49.5個月。誘導化療也改善生存率（風險比例為0.24；p = 0.022）和無遠處轉移生存率（風險比例為0.24；p = 0.024）。兩組的局部區域控制率相若（66%比53%；p = 0.191）。

結論：我們的小型回顧研究顯示誘導化療能改善IVA期口腔癌患者的生存率和無遠處轉移生存率。

INTRODUCTION

The current treatment of choice for operable locally advanced squamous cell carcinoma (SCC) of the oral cavity (OC) is curative surgery followed by adjuvant radiotherapy or chemo-radiotherapy.[1] Despite such aggressive treatment, overall survival (OS) remains dismal; the 5-year OS of patients with stage IVA disease (T1-3N2, T4aN0-2) ranges from 41.3% in T4aN0 to 15.8% in T4aN2.[2] A high locoregional failure rate and modest distant metastasis rate both contribute to the low survival rate.[3]

Neoadjuvant chemotherapy (NC) given early prior to definitive local therapy of either surgery or radiotherapy may shrink the primary or nodal tumour, potentially facilitating local control by surgery or local radiotherapy, and may theoretically improve control of occult distant metastases and long-term survival. In a phase III randomised controlled trial investigating the role of NC with docetaxel-cisplatin–5-fluorouracil (TPF) in a group of 256 patients with locally advanced stage III or IVA operable SCC of the OC, those with more advanced, clinically N2 disease had improved OS (hazard ratio [HR] 0.466; p = 0.044) and distant metastasis-free survival (HR 0.468; p = 0.046) with NC.[4] Although the results from another study that included patients with earlier-stage disease and the use of neoadjuvant cisplatin–5-fluorouracil (PF) chemotherapy were negative,[3] a pooled analysis of individual patient data derived from these two large trials yielded favourable results in the subset of cN2 patients, consolidating the role of NC in this patient subgroup, especially when TPF was used.[5]

As the waiting time for definitive surgery can vary in busy local public hospitals in Hong Kong, upfront NC has the additional advantage of arresting tumour growth while awaiting surgery, particularly in those with marginal resectability. We report our single-institution experience of TPF NC given prior to definitive surgery and other adjuvant locoregional treatment in a cohort of patients with resectable stage IVA SCC of the OC.

METHODS

All consecutive patients with SCC of the OC treated in our institution from April 2012 to April 2015 were retrospectively reviewed. Among 69 patients identified during the study period, 11 with stage IVA SCC OC received TPF NC. The treatment strategy of employing TPF NC before definitive surgery was formulated by the institution's head and neck cancer multidisciplinary team. TPF NC was planned for four patients who had a

marginally operable tumour. Seven other patients had operable tumour but were scheduled to receive NC as an interim measure while awaiting definitive surgery. The OC SCCs in all patients were histologically confirmed. Radiological imaging by either computed tomography or magnetic resonance imaging was performed before and after NC for staging and response assessment. Outcomes of patients in the neoadjuvant group were compared with 11 age-matched patients with stage IVA SCC of OC who received no NC before curative surgery and adjuvant treatment during the same period (control group).

TPF NC was given once every 3 weeks for three cycles in most patients until definitive surgery. The schedule of chemotherapy was as follows: docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 both infused on day 1, and 5-fluorouracil 750 mg/m^2 infused over 120 hours from days 1 to 5.[6] Prophylactic levofloxacin 500 mg daily was given for 10 days, from day 5 to 14. Primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) support was not mandatory.

Definitive surgery was performed at around 4 weeks from day 1 of the last cycle of NC. Adjuvant radiotherapy with or without concurrent chemotherapy was given to all patients except those who had received prior head and neck radiation when a second course of radiotherapy was relatively contraindicated. All patients were treated by intensity modulated radiotherapy to the primary tumour bed and / or cervical lymphatic regions judged to harbour potential microscopic disease following the curative surgery, to at least 60 Gy in 30 fractions over 6 weeks. For those deemed to be at high risk of further relapse (involved margin and / or extracapsular extension in metastatic lymph nodes), a total radiotherapy dose of 66 Gy in 33 daily fractions over 6.5 weeks was delivered to areas at risk, concurrent with cisplatin chemotherapy (100 mg/m^2 on days 1, 22, and 43).

Demographic and clinical details of the 22 patients are summarised in Table 1. Treatment toxicity data of the NC were reported and based on CTCAE (Common Terminology Criteria for Adverse Events) version 4.0.[7] Radiological response of NC was assessed using the RECIST (Response Evaluation Criteria In Solid Tumours).[8] Presence of and time to locoregional relapse, distant metastases and survival events were recorded, computed, and compared for the two groups. For statistical analysis, categorical data were compared by Fisher's exact test, continuous data by Mann-Whitney *U* test, and survival data by log rank test. Retrieval of clinical and outcome data was last performed on 1 August 2017.

The study was approved by the institution's Ethics Committee (Ref: KC/KE-17-0209/ER4) and was conducted in compliance with the Declaration of Helsinki.

RESULTS

Baseline patient demographics including age, gender, disease subsite, T stage, N stage, retreatment, and surgical margin status did not differ between the two groups (Table 1). According to TNM staging, 86.4% of our patients had N2 disease (90.9% in the neoadjuvant group vs. 81.8% in the control group, p = 1). The median longest dimension of the primary tumour and that of the metastatic lymph node(s) was larger in the neoadjuvant group (primary, 3.0 cm vs. 2.4 cm, p = 0.014; lymph node, 1.0 cm vs. 0.6 cm; p = 0.022) [Table 1]. All 11 patients in the neoadjuvant group completed three cycles of NC without delay. Prophylactic G-CSF was given in two (18.2%) patients at the patient's request or based on the oncologist's risk assessment.

Chemotherapy toxicities were generally tolerable and no dose reduction was required in any patient. Docetaxel allergy was observed in one (9.1%) patient during cycle two and docetaxel was omitted in the subsequent cycle. Haematological toxicity was relatively infrequent. Grade 3 anaemia not requiring transfusion and neutropenic fever was observed in one patient each (9.1%). The patient with neutropenic fever received G-CSF support and a full dose of two subsequent cycles of chemotherapy. There was no treatment-related mortality.

Response was assessed by comparing the results of radiological examination before and after NC prior to surgery. Clinical complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were observed in one (9.1%), five (45.5%), three (27.3%) and two (18.2%) patients, respectively. The overall response rate was 54.5%.

All patients in the neoadjuvant group underwent curative surgery as planned, including the five patients who were deemed to be non-responders (SD and PD). Complete (R0) resection was achieved in 10 (90.9%) patients; one patient had a focally involved micro-

Table 1. Baseline clinicopathological characteristics of study groups.

Demographics	Neoadjuvant chemotherapy (n = 11)	No neoadjuvant chemotherapy (n = 11)	p Value
Median (range) age, y	55 (32-65)	56 (40-69)	0.375*
Gender			
Male	6 (54.5%)	5 (45.5%)	0.67†
Female	5 (45.5%)	6 (54.5%)	
Disease subsite			
Tongue	10 (90.9%)	10 (90.9%)	1†
Alveolus	1 (9.1%)	1 (9.1%)	
T stage			
cT1-3	8 (72.7%)	8 (72.7%)	1†
cT4	3 (27.3%)	3 (27.3%)	
Median (range) of longest dimension of primary tumour, cm	3.0 (2.1-5.4)	2.4 (1-3.4)	0.014*
N stage			
cN0-1	1 (9.1%)	2 (18.2%)	1†
cN2	10 (90.9%)	9 (81.8%)	
Median (range) of longest dimension of lymph node, cm	1.0 (0.8-2.4)	0.6 (0.3-1.2)	0.022*
Staging method			
PET/CT or CT thorax/abdomen	7 (63.6%)	7 (63.6%)	1†
Others (e.g. USG liver/CXR)	4 (36.4%)	4 (36.4%)	
Retreatment			
Relapsed	2 (18.2%)	2 (18.2%)	1†
Newly presented	9 (81.8%)	9 (81.8%)	
Margin			
Not involved	8 (72.7%)	8 (72.7%)	1†
Close (≤4 mm)	2 (18.2%)	2 (18.2%)	
Involved	1 (9.1%)	1 (9.1%)	

Abbreviations: CT = computed tomography; CXR = chest X-ray; PET = positron emission tomography; USG = ultrasound.
* Mann-Whitney *U* test.
† Fisher's exact test.

scopic surgical margin. Extracapsular extension to the pathologically involved lymph node(s) was observed in three (27.3%) patients. One (9.1%) patient who had a radiological PR had pathological CR (pCR). The patient with radiological CR had a good pCR, with pathological downstaging from cT2N2b to ypT1N0.

With the exception of two patients who previously received radiotherapy to the head and neck region for prior tongue cancer and lymphoma respectively, all other nine (81.8%) patients in the neoadjuvant group proceeded to postoperative adjuvant treatment. Six (54.5%) patients received adjuvant radiotherapy alone and three (27.3%) received adjuvant chemo-radiotherapy. Among the three patients who received chemo-radiotherapy using 3-weekly cisplatin following NC and surgery, one completed all three cycles of concurrent chemotherapy and two experienced a 1-week delay after the first cycle of concurrent chemotherapy and therefore received only two cycles during radiotherapy.

At a median follow-up period of 49.5 months among the 22 patients in the two cohorts, the OS was significantly improved in those with TPF NC (HR 0.24, median survival not reached vs. 12 months; p = 0.022) [Figure 1]. Distant relapse-free survival was also significantly improved with NC (HR 0.24, median survival not reached vs. 9.5 months; p = 0.024) [Figure 2]. Locoregional control rates were not significantly different between the two groups (66% with NC vs. 53% without NC; p = 0.191) [Figure 3].

DISCUSSION

The benefit of delivering NC before definitive surgery in advanced cancer of the OC is controversial. Conflicting results have been reported by various randomised controlled clinical trials designed with different inclusion criteria to test different chemotherapeutic regimens; results from meta-analyses were also inconsistent (Table 2).[3-5,9,10] The definitions of locally advanced cancer and therefore the population of patients included in these studies were heterogeneous, ranging from cT2N0 (>3 cm) to cT4N3.[3,4] TPF has been shown to be superior to PF in multiple clinical trials and this was also confirmed in a meta-analysis using individual

patient data.[11,12] According to this meta-analysis, TPF significantly improved OS (HR 0.72, 95% confidence interval [95% CI] = 0.63-0.83), locoregional failure (HR 0.79, 95% CI = 0.66-0.94), and distant metastases (HR 0.63, 95% CI = 0.45-0.89) when compared with PF given before local radiotherapy or chemo-radiotherapy.[12]

For patients with operable locally advanced OC cancer, efforts have also been made to identify the subgroup of patients who may benefit more from NC. As well as the study reported by Zhong et al[4] that suggested improved distant metastasis-free survival and OS in a cN2 subgroup, an updated meta-analysis performed on individual patient data obtained from two large studies (one using PF and another using TPF) has also confirmed such findings.[5] These results indicate that although the overall population of stage III and IVA disease may not benefit from NC, patients with

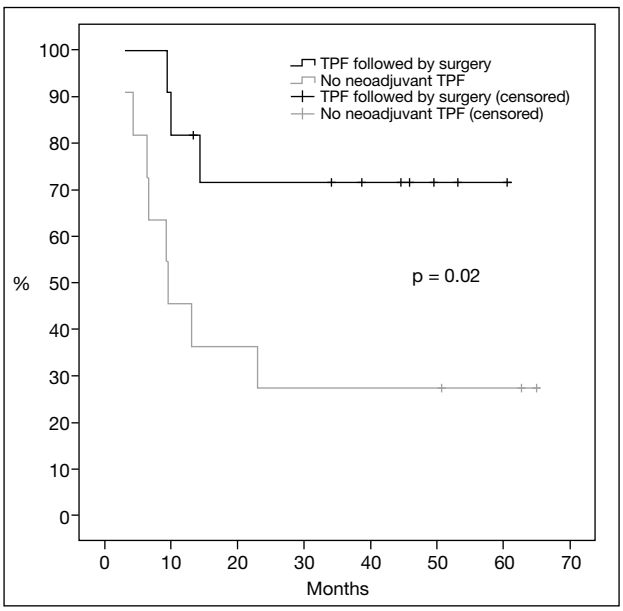

Figure 2. Distant relapse-free survival for patients with or without neoadjuvant chemotherapy.
Abbreviation: TPF = docetaxel-cisplatin–5-fluorouracil.

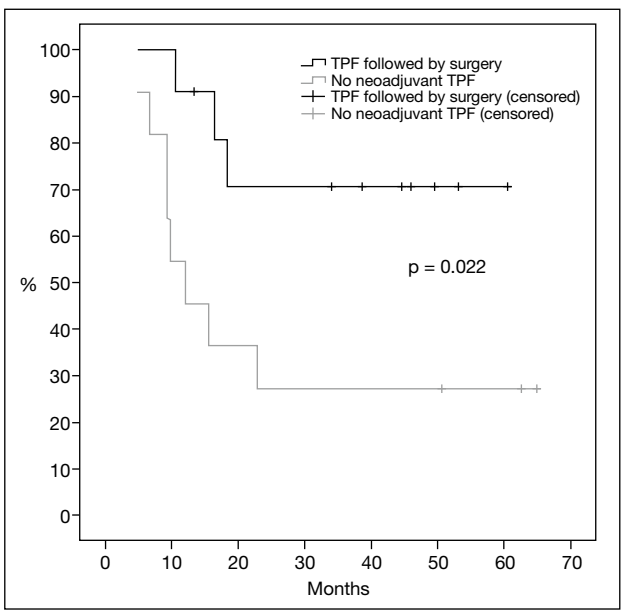

Figure 1. Overall survival for patients with or without neoadjuvant chemotherapy.
Abbreviation: TPF = docetaxel-cisplatin–5-fluorouracil.

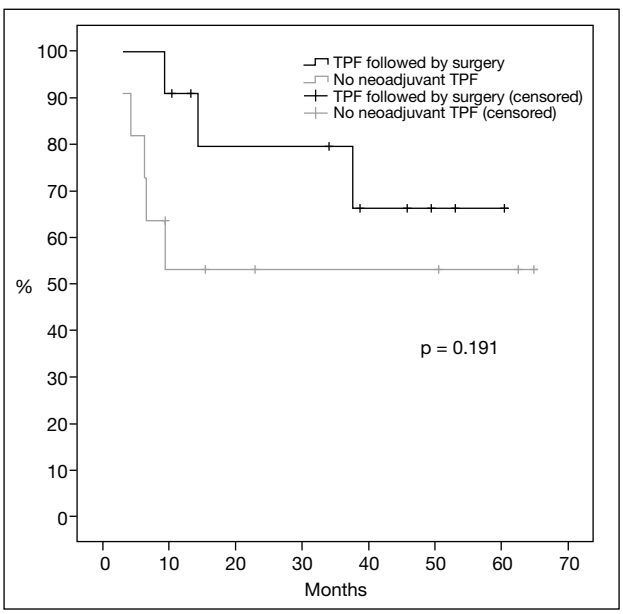

Figure 3. Locoregional control rates for patients with or without neoadjuvant chemotherapy.
Abbreviation: TPF = docetaxel-cisplatin–5-fluorouracil.

Table 2. Overview of meta-analyses to evaluate neoadjuvant chemotherapy before definitive treatments for patients with squamous cell carcinomas of the oral cavity.

Study	Definitive treatment received	No. of patients	Overall survival*	Disease-free survival*	Distant metastases rate*
Blanchard et al, 2011[9]	Radiotherapy	4331 (Individual patient data)	0.87 (0.80-0.93)†	NA	NA
Marta et al, 2015[5]	Surgery	451 (Individual patient data)	1 (0.88-1.13)	1.04 (0.90-1.20)	1.04 (0.90-1.20)
Lau et al, 2016[10]	Radiotherapy or surgery	2872 (in 6 Trials)	0.95 (0.85-1.05)	1.05 (0.92-1.21)	1.05 (0.92-1.21)

Abbreviation: NA = not available.
* Data are shown as hazard ratio (95% confidence interval).
† Statistically significant.

more regionally advanced cN2 tumours could benefit, reiterating the importance of patient selection for NC.

Our study reported the outcome of NC in the above-mentioned high-risk group of patients for whom aggressive systemic treatment was expected to be particularly useful. With all patients being stage IVA and 91% patients of our small neoadjuvant cohort had cN2 disease, NC with TPF followed by surgery and adjuvant treatment could reduce distant relapse and improve OS, although locoregional control was not improved. OS at 4 years was 70% after neoadjuvant TPF, and 45.4% without NC. These rates were numerically comparable with disease- and stage-matched OS reported by Marrone et al,[2] but were numerically inferior to the results reported by some randomised studies (Table 3[3,11,13-15]), possibly due to the inclusion of patients with more advanced disease in our study.

Apart from patients with cN2, patients who achieve pCR may also benefit more from NC, both in terms of locoregional control and OS.[3] In the same study, pCR rate was higher in patients who presented with earlier-stage disease: 41% stage II, 50% stage III, and 9% stage IV.[3] The only patient with pCR in the neoadjuvant group of our study remained alive and disease-free for almost 3 years. Apart from clinical stage, other predictive markers for pCR have been studied. In patients treated with neoadjuvant PF, presence of a non-functioning p53 mutation was significantly associated with non-response.[16] For patients treated with TPF, high cyclin D1 expression and high growth differentiation factor 15 expression were associated with prolonged OS and distant metastasis-free survival, for cN2 and cT3-4N0 patients respectively.[4,17,18] Further validation of these markers is eagerly awaited to better inform oncologists and patients before embarking on NC.

Despite reporting a lower pCR rate of 13.4%, Zhong et al[15] defined another group of patients who had a favourable pathological response with minimal residual disease, if only scattered foci of tumour cells were found after NC (<10% of viable tumour cells). Improved OS, disease-free survival, locoregional recurrence-free survival, and distant metastasis-free survival were observed in these 27.7% of patients who had favourable pathological responses.[15] Further studies are required to confirm the role of a favourable pathological response as an independent predictor of various survival endpoints.

Given the possibility of achieving significant clinical response or even pCR after NC, it remains debatable whether de-escalating the mutilating surgery is safe or feasible. Fewer patients were reported to require mandibulectomy with the use of NC (31% vs. 52%, p value not specified) in a randomised study, although the indication for mandibulectomy was not specified nor stratified at randomisation.[19] In the same study,

Table 3. Overall survival across trials including oral cancer patients using neoadjuvant chemotherapy.

Study	No. of oral cancer patients	Stage	Chemotherapy regimen	Definitive treatment received	Median follow-up, mo	Rough point estimates of overall survival
Zhong et al (2012), phase III RCT[15]	256 (100%)	III-IV (34.4% stage IVA)	TPF vs. no neoadjuvant	Surgery and adjuvant radiotherapy	30	~65% in both groups at 30 months, NS
Bossi et al (2014), phase III RCT[3]	198 (100%)	II-IV (34.4% stage IVA)	PF vs. no neoadjuvant	Surgery and adjuvant radiotherapy	138	46.5% vs. 37.7% at 120 months, NS
Present study	22 (100%)	IV (all)	TPF vs. no neoadjuvant	Surgery and adjuvant radiotherapy ± concurrent chemotherapy	49.5	70% vs. 45.5% at 48 months, p = 0.022
Hitt et al (2014), TTCC phase III RCT[13]	93 (21.2%)	IV (97.8% of oral cancer patients)	TPF vs. PF vs. no neoadjuvant	CCRT	22.1-23.8	~50% for all three groups at 24 months, NS
Haddad et al (2013), PARADIGM phase III RCT[14]	26 (17.9%)	IV (85.5% of all patients)	TPF vs. no neoadjuvant	CCRT	49	~65% in both groups at 48 months, NS
Posner et al (2007), TAX324 phase III RCT[11]	71 (14.2%)	IV (82.4% of all patients)	TPF vs. PF	CCRT	42	62% vs. 48% at 36 months, p = 0.002

Abbreviations: CCRT = concurrent chemo-radiotherapy; NS = not significant; PF = cisplatin–5-fluorouracil; RCT = randomised controlled trial; TPF = docetaxel-cisplatin–5-fluorouracil.

pathological downstaging also reduced the number of patients who required adjuvant radiotherapy in the neoadjuvant arm, possibly contributing to reduced long-term toxicity such as neck fibrosis and dysphagia.[19] Nonetheless this benefit may not be observed if the need for adjuvant radiotherapy is decided a-priori according to disease staging before treatment, as observed in Zhong et al's study[15] and the current study.

The pattern and prevalence of toxicity of TPF have been extensively reported in the literature. Haematological toxicity is the most frequent toxicity reported, with febrile neutropenia reported in 2% to 23% of patients. The rate of febrile neutropenia was generally lower in studies that used dose-reduced TPF, and showed no definite relationship with the presence or absence of G-CSF prophylaxis. The rate of febrile neutropenia observed in our study was largely comparable to those of other reports[11,13-15]; all our patients were able to complete the planned three courses of TPF NC.

Although radiological progression was observed in two (18.2%) patients following NC, feasibility of complete resection was not adversely affected. All patients were able to proceed to their planned further surgery and then adjuvant radiotherapy, if not contraindicated by a history of radiation. This was consistent with the reports of Zhong et al[15] and Licitra et al[19] in that no or very few patients became inoperable after deferring definitive surgery for a finite period of a few cycles of NC. Moreover, all three patients scheduled for postoperative adjuvant chemo-radiotherapy could receive at least two cycles of the planned three cycles of cisplatin chemotherapy given concurrently with radiotherapy.

This study showed that patients with operable locally advanced stage IVA SCC of OC, especially those with cN2 tumours, benefited from NC with reduced distant relapse and prolonged OS. This suggests that NC with TPF can serve as a bridging therapy to contain tumour proliferation in patients with locally advanced oral cancers during the variable period awaiting surgery and may also be considered specifically in cN2 patients with a view to improving distant control and OS.

To minimise potential selection bias, our study included all consecutive patients with OC cancers managed by our institution during the study period. Index patients treated by NC were retrospectively matched with patients treated by upfront surgery without NC according to disease stage and age. Many patients in the control group had received surgery without NC at other hospitals prior to referral to our institution, and they were treated according to our institutional protocol for standard postoperative radiotherapy or chemo-radiotherapy. The surgical margin status was comparable across groups, indicating comparable surgical quality. Nonetheless the number of patients reported in the study was relatively small and there may have been an unequal distribution of prognostic factors other than those compared in the two cohorts. The retrospective nature of this study may have led to underreporting of subtle toxicity of lower grade (grade 1 or 2).

CONCLUSION

Compared with standard upfront surgery followed by adjuvant treatments, administration of TPF NC before definitive surgery in a small cohort of stage IVA SCC of the OC achieved better distant relapse-free survival and OS. This is consistent with other published results.

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