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ORIGINAL RESEARCH

The oncological outcome and influence of neoadjuvant chemotherapy on the surgery in the resectable and locally advanced oral squamous cell carcinoma

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Aim: The role of neoadjuvant chemotherapy (NCT) in the treatment of advanced oral squamous cell carcinoma (OSCC) is still controversial. Especially, there are still few studies investigating the influence of NCT on the following surgery. In this retrospective single-center attended cohort study, we investigated the oncological effect of NCT and its influence on the following surgery in patients with resectable locally advanced OSCC.

Method: The clinical data of 88 patients with locally advanced but resectable OSCC (T3/4) were reviewed retrospectively. NCT plus conservative surgery and radical surgery were compared. Five-year disease-specific survival (DSS) was observed as the main endpoint.

Results: Among 88 patients enrolled in this study, 56 patients received upfront radical surgery (non-NCT group) and 32 patients received NCT followed by surgery (NCT group). The patients in the non-NCT group had a statistically better DSS than the patients in the NCT group (P=0.041). Twenty-one out of 32 (65.6%) patients who received NCT were good responders including two patients (6.2%) had a complete response and 19 patients (59.4%) had a partial response. There was no statistical difference between good and poor responders in 5-year DSS (P=0.823). Eleven patients (34.4%) had conservative surgery without flap reconstruction and 21 patients had radical surgery with flap reconstruction after NCT. No statistical difference in surgical margins was found between the two types of surgery (P=0.519). There was also no statistical difference in 5-year DSS between the two types of surgery (P=0.652).

Conclusion: NCT plus surgery could not improve survival compared with upfront surgery. NCT could modify the surgical extent but would not affect the surgical margins. This conclusion should be explained cautiously, and randomized clinical trials with large sample size were needed to further answer the question.

Keywords: neoadjuvant chemotherapy, oral squamous cell carcinoma, locally advanced, surgery, survival

Introduction

Oral squamous cell carcinoma (OSCC) is a common malignant head and neck tumor with approximately 300,000 new cases worldwide per year. The mainstay treatment of OSCC is surgery-centered multimodality therapy. Reconstructive surgery is always needed to restore the oral function after ablative surgery.[1] Following the advances in imaging and therapies, the prognosis of patients with OSCC has improved, with its 5-year survival rate arriving at about 70% recently.[2]

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Neoadjuvant chemotherapy (NCT) refers to chemotherapy administered before surgery.[3] Its role in the treatment of head and neck cancers is still controversial.[4–6] Two main concerns for the application of systemic therapy are the improvement of long-term survival and organ/function preservation. Induction chemotherapy (before radiotherapy) was firstly started in laryngeal cancer in order to select appropriate patients for organ preservation therapy. Then, questions were asked whether an addition of chemotherapy before surgery or radiotherapy could improve survival. The answers were still not clear even after a lot of studies including randomized clinical trials and meta-analysis.[7–11] In addition, there are still few studies investigating the influence of NCT on the following surgery. Can we perform a limited surgery after NCT? Will it affect the surgical margins and prognosis? Further studies are necessary to evaluate NCT in the treatment of OSCC.

In this study, we retrospectively reviewed a group of patients with locally advanced but resectable OSCC in a single cancer center. Comparison between NCT plus conservative surgery and radical surgery was done to investigate the influence of NCT on surgery and its oncological outcome.

Methods

Study design and screening of patients

This was a retrospective and observational study. The study was approved by the institutional review board at the Sun Yat-Sen University Cancer Center (IRB: GZR2018-188) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients at their first visit. We comprehensively reviewed the clinical records of OSCC patients who were treated in Sun Yat-Sen University Cancer Center during January 1, 2003 and December 30, 2011. All the included patients were resided in Southern China. Finally, a total of 88 patients who received NCT followed by surgery or surgery without NCT and met the inclusion criteria were included in this study. The inclusion criteria were as follows: 1) Previously untreated, resectable T3 or T4 OSCC without distant metastasis; and 2) all patients received surgery for cure. Staging workup included direct laryngoscopy, tumor biopsy, and computed tomographic imaging. Patients with clinical or radiographic evidence of bone involvement (referred to distant metastasis involved the sternum, the vertebrae and other bones not located in head and neck) or a Karnofksy performance status of less than 60% were ineligible. The patients with preoperative radiotherapy or postoperative chemotherapy were not included. The site and extent of the tumors were evaluated by clinical examination and imaging scans.

Subgroups

NCT followed by surgery and surgery without NCT are two main treatments for resectable T3 or T4 OSCC without distant metastasis in the clinical practice. The patients were retrospectively classified as NCT and non-NCT subgroups according to their different treatments. The grouping structure was illustrated in Figure 1. NCT group referred to the patients who received preoperative NCT followed by surgery and postoperative radiotherapy if indicated. Non-NCT group referred to the patients who received upfront surgery followed by postoperative radiotherapy if indicated.

Treatments

Neoadjuvant chemotherapy

The patients in the NCT group received two cycles of preoperative NCT. TPF regimen (docetaxel 60 mg/m^2 intravenously on day 1, followed by cisplatin 75 mg/m^2 intravenously on day 1, followed by fluorouracil 750 mg/m^2 per day as a 120-hr continuous intravenous infusion on days 1 through 5) was administered every 3 weeks. Supportive measures including dexamethasone, antiemetics, and hydration/diuretics were also administered. Primary prophylaxis with recombinant granulocyte colony-stimulating factor was prescribed 48 hrs after the chemotherapy. Chemotherapy dose reductions were allowed for grade 3–4 hematologic, GI or renal toxicities occurring after cycle one.

Surgery

Radical surgery with flap reconstruction or conservative surgery without flap reconstruction was alternative surgery for the patients. In the non-NCT group, upfront radical surgery was performed. Neck dissection and flap reconstruction were also done. In the NCT group, the choice of conservative or radical surgery is not merely determined by the response of NCT. Multiple aspects patient's clinical manifestations were also considered, such as primary site of tumor, pathology differentiation, T and N stages, and shape of tumor. Surgery was performed at least 2 weeks after completion of NCT. Tumor size and invasion range may shrink after NCT treatment,

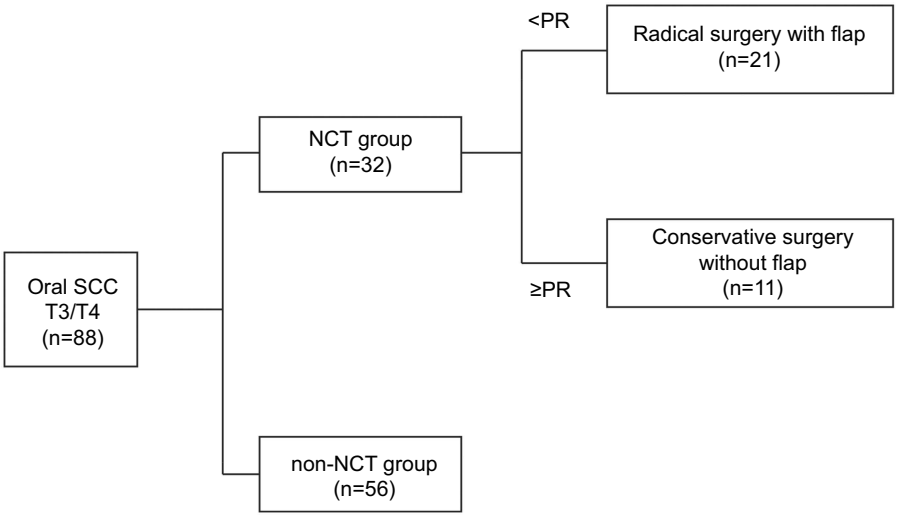

Figure 1 Flow chart for the patient grouping in this study.

excessive medical treatment may be applied and the physical function may be impaired if the same surgical extent as non-NCT patients was applied to the patients who received NCT treatment. Therefore, the surgical extent is partly determined by the response after NCT. For radical surgery with flap reconstruction, wide excision of the primary lesion with 1-cm surgical margin and neck dissection were performed. Microvascular free flap or pedicled pectoralis major flap were used to reconstruct the defects after radial surgery. For conservative surgery without flap reconstruction, the surgical extent was reduced to preserve the oral function after NCT. When the defect after conservative surgery was small, no flap reconstruction was needed.

Postoperative radiotherapy

Adjuvant treatment after surgical extirpation was determined on the basis of standard PORT criteria, including extracapsular spread, positive margins, regional metastasis, and perineural invasion. Postoperative radiotherapy was initiated 4–6 weeks after surgery for the patients with adverse features. Standard conformal or intensity-modulated radiotherapy was administered at a dose of 1.8–2 Gy per day, 5 days per week, for 6 weeks (54–60 Gy in total).

Assessments

The stage of OSCC was evaluated according to the UICC TNM (8^{th} edition). Clinical tumor response was evaluated 2 weeks after NCT by physical examination and imaging scan. The standard World Health Organization (WHO) criteria were used to evaluate the response after NCT. Patients with a response of at least 50% (more than partial response, PR) were classified as good responders. Toxicities were assessed weekly during and after completion of NCT according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Surgical margins were evaluated pathologically by inoperative frozen section and postoperative HE staining section.

Follow-up and outcomes

All the patients were followed up for at least 5 years, monitored every 3 months during the first 2 years, every 6 months during the subsequent 3–5 years, and once per year thereafter until death. The primary outcomes of interest were disease-specific survival (DSS). DSS was defined as the time from treatment to the time of death from OSCC.

Statistical analysis

For descriptive analysis, categorical data were expressed as number and percentage. The baseline data in the two subgroups were compared by the Chi-square test to assess differences among the clinical variables. The Kaplan–Meier method and the log-rank test were used to assess differences in the survival between different treatment subgroups. IBM SPSS statistics software (version 17.0) was used to perform the statistical analysis. A two-tailed $P<0.05$ was considered statistically significant.

Results

Baseline data of the patients

Among 88 patients enrolled in this study, 56 patients received upfront radical surgery (non-NCT group) and 32

Table 1 Clinical data of NCT and non-NCT cohorts

Parameters		Non-NCT (n=56)(%)	NCT (n=32)(%)	Total (n=88)(%)	*P*
Sex					
	Male	42 (75.0)	24 (75.0)	66 (75.0)	1.000
	Female	14 (25.0)	8 (25.0)	22 (25.0)	
Age					
	Range (median)	28–91 (60)	22–74 (58)	22–91 (59)	0.361
	≦40	6 (10.7)	7 (21.9)	13 (14.8)	
	41–60	23 (41.1)	12 (37.5)	35 (39.8)	
	≧61	27 (48.2)	13 (40.6)	40 (45.5)	
Pathology differentiation					
	Poor	2 (3.6)	2 (6.2)	4 (4.5)	0.680
	Moderate	11 (19.6)	8 (25.0)	19 (21.6)	
	Well	43 (76.8)	22 (68.8)	65 (73.9)	
T					
	T3	32 (57.1)	19 (59.4)	51 (58.0)	0.838
	T4	24 (42.9)	13 (40.6)	37 (42.0)	
N					
	N0	30 (53.6)	13 (40.6)	43 (48.9)	0.357
	N1	12 (21.4)	10 (31.2)	22 (25.0)	
	N2	14 (25.0)	8 (25.0)	22 (25.0)	
	N3	0 (0)	1 (3.1)	1 (1.1)	
Surgical margin					
	+	10 (17.9)	8 (25.0)	18 (20.5)	0.424
	–	46 (82.1)	24 (74.0)	70 (79.5)	

patients received NCT followed by surgery (NCT group). The baseline data of the two groups were shown in Table 1. There was no statistical difference in clinical features between the two groups.

DSS between NCT and non-NCT group

We compared the (DSS) between NCT and non-NCT group. Kaplan–Meier analysis showed that the patients in the non-NCT group had a statistically better DSS (71.4% 5-year OS) than the patients in the NCT group (50.0% 5-year OS) (*P*=0.041). Their survival curves are shown in Figure 2. The patients received upfront radical surgery would have a better prognosis than the patients received NCT followed by surgery.

NCT response

Twenty-one out of 32 (65.6%) patients who received NCT were good responders including two patients (6.2%) had a complete response (CR) and 19 patients (59.4%) had a PR (Table 2). We compared DSS between good responders and poor responders. Although the patients with good response had a little bit better prognosis (52.4% 5-year DSS), Kaplan–Meier analysis showed no statistical difference than the patients with a poor response (45.5% 5-year DSS) (*P*=0.823). The survival curves are shown in Figure 3.

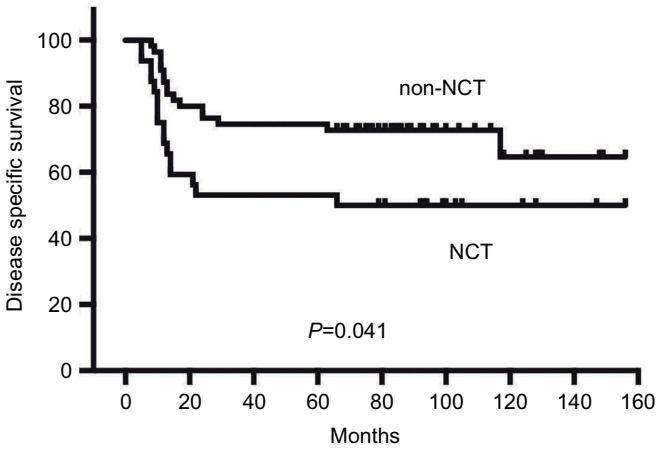

Figure 2 Disease specific survival between NCT and non-NCT groups.

Table 2 Clinical data of the patients treated with conservative and radical surgery in the NCT subgroup

Parameters		Conservative surgery (n=11)(%)	Radical surgery (n=21)(%)	Total (n=32)(%)	*P*
Sex					
	Male	8 (72.7)	16 (76.2)	24 (75.0)	0.830
	Female	3 (27.3)	5 (23.8)	8 (25.0)	
Gender					
	Range (median)	33–74 (48)	22–71 (59)	22–74 (58)	0.794
	21–40	2 (18.2)	5 (23.8)	7 (21.9)	
	41–60	5 (45.5)	7 (33.3)	12 (37.5)	
	61–80	4 (36.4)	9 (42.9)	13 (40.6)	
Primary site					
	Tongue	9 (81.8)	11 (52.4)	20 (62.5)	0.387
	Gingiva	1 (9.1)	5 (23.8)	6 (18.8)	
	Buccal	0 (0)	3 (14.3)	3 (9.4)	
	Floor	1 (9.1)	1 (4.8)	2 (6.2)	
	Palate	0 (0)	1 (4.8)	1 (3.1)	
Pathology differentiation					
	Poor	0 (0)	2 (9.5)	2 (6.2)	0.114
	Moderate	5 (45.5)	3 (14.3)	8 (25.0)	
	Well	6 (54.5)	16 (76.2)	22 (68.8)	
T					
	T3	7 (63.6)	12 (57.1)	19 (59.4)	0.722
	T4	4 (36.4)	9 (42.9)	13 (40.6)	
N					
	N0	8 (72.7)	5 (23.8)	13 (40.6)	0.029
	N1	3 (27.3)	7 (33.3)	10 (31.2)	
	N2	0 (0.0)	8 (38.1)	8 (25.0)	
	N3	0 (0.0)	1 (4.8)	1 (3.1)	
Response					
	CR	2 (18.2)	0 (0)	2 (6.2)	0.160
	PR	7 (63.6)	12 (57.1)	19 (59.4)	
	MR	1 (9.1)	5 (23.8)	6 (18.8)	
	SD	1 (9.1)	4 (19.0)	5 (15.6)	
Surgical margin					
	+	2 (18.2)	6 (28.6)	8 (25.0)	0.519
	–	9 (81.8)	15 (71.4)	24 (75.0)	

Influence of NCT on the following surgery

Among 32 patients received NCT, 11 patients (34.4%) had conservative surgery without flap reconstruction and 21 patients had radical surgery with flap reconstruction. The choice of conservative or radical surgery is not merely determined by the response of NCT. Multiple aspects patient's clinical manifestations as suggested in Table 2 were also considered, such as primary site, pathology differentiation, T stage, and N stage. We compared the surgical margins between the patients received conservative surgery and radical surgery. 2/11(18.2%) and 6/21 (28.6%) patients had positive surgical margins, respectively. Chi-square test showed no statistical difference between the two types of surgery (P=0.519) (Table 2).

We further analyzed the influence of different surgical extent on the DSS in the patients who received NCT. Although the patients who received conservative surgery without flap reconstruction had a better prognosis (54.5% 5-year DSS), Kaplan–Meier analysis showed no statistical

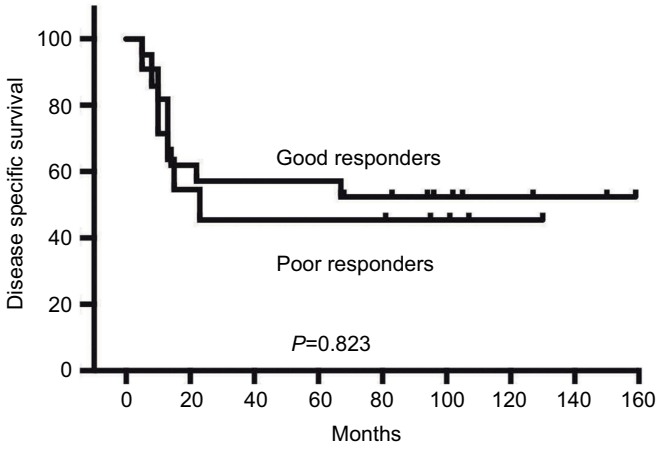

Figure 3 Disease specific survival between good responders and poor responders.

difference than the patients who received radical surgery with flap reconstruction (47.6% 5-year DSS) (P=0.652) (see Figure 4).

Discussion

The main treatment for oral cancers was surgery with postoperative radiotherapy. In the current study, 88 patients diagnosed as T3/4 OSCC all received surgery. Considering the postoperative functional impairment, preoperative NCT was applied to 32 patients in order to downstage the disease. Fifty-six patients admitted during the same period to receive standard therapy were compared. The two groups were balanced in the clinical features. From this retrospective cohort study, we would like to know the clinical value of NCT in advanced OSCC. The results might be used as the preliminary data for further randomized clinical trials.

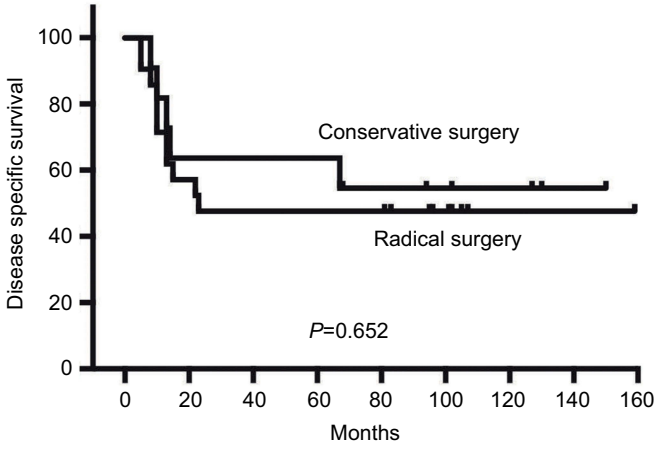

Figure 4 Disease specific survival between conservative surgery and radical surgery.

The role of the NCT in the treatment of advanced OSCC is still not clear now. Following the concept of functional preservation in laryngeal cancers, NCT was also used in oral cancers. However, because the reconstructive surgery was very successful in maintaining postoperative oral function, the application of NCT was not clearly indicated in this situation. Another indication was whether the addition of NCT could improve the survival of advanced oral SCCs. The data of the current retrospective study showed that upfront surgery would have better survival than NCT in the treatment of advanced T3/4 OSCC. Another retrospective study by Chinn et al, also had the same result. Two randomized clinical trials for advanced resectable OSCC in the literature confirmed the absence of survival benefit with preoperative NCT.[8,9] In addition, other randomized clinical studies of inductive chemotherapy before radiotherapy also showed no survival benefit for the patients with advanced head and neck cancers.[10–12] These studies sent a clear message that whether chemotherapy was added before surgery (neoadjuvant) or concurrent chemoradiation (inductive), there would be no survival benefit for advanced head and neck cancers.

NCT was often considered in clinical scenario as a way to select good responders for further local therapy and sometimes interpreted as a marker with good prognosis. The response rate after induction chemotherapy was different in the literature. Regimen, dosage, target patients, HPV status, and staging, etc. were all the factors influencing the response. TPF regimen was reported with the highest good response rate as 94%.[7,8,13,14] A good response rate in this study was around 66% (21/32). In order not to affect the following surgery, the dosage of docetaxcel was reduced (60 mg/m^2 intravenously on day 1) to prevent from severe neutropenia. No patients postponed their surgery in the current study. Compared with other studies,[7–9,13,14] the CR rate was only around 6% in our study. The lower dosage was possibly a decisive factor. Our results showed that good responders did not translate into better prognosis than poor responders. However, the pathological complete response (pCR) was reported a linkage with a good prognosis,[8,9,15] although the pCR rate was still very low. The future studies might focus on the selection of these patients who had a high possibility to benefit from NCT. Perrone et al, reported that normal p53 function might predict pCR after cisplatin-based NCT in oral cancer.[16] Biological markers could play an important role in predicting the response after NCT.

NCT could shrink the tumor bulk in good responders. Then, whether the following surgery could be modified in good responders with oral cancer was a clinical question. Lee et al, reported that limited surgery was comparable with radical surgery after NCT in the mouse model.[17] Although NCT could not improve long-term survival, a limited surgery without a free flap reconstruction in good responders was also a favorable outcome. In this study, we analyzed the influence of NCT on the surgical parameters including surgical margins and extent. 34.4% of the patients in our study received conservative surgery after NCT. The data showed that a limited surgery would not compromise the surgical margin and could gain a comparable survival rate with radical surgery. We thought the benefit for patients treated with NCT followed by conservative surgery in good responders was direct closure of the surgical defects and prevention from a complicated reconstruction with free flaps.

The weakness of this study was the retrospective study design and a small sample size. Our policy was that good responders after NCT would receive conservative surgery; however, there were two patients with poor response still received conservative surgery because of a strong subjective intention to evade major reconstructive surgery. At the same time, 12 patients with PR response still received radical surgery. The retrospective design could not rule out these systemic interferences. The explanation of the result in this study should be cautious, especially in the influence of NCT on the following surgery. In addition, depth of invasion of the tumor and tumor budding has been the interesting topics in this field now. It is a pity that this retrospective study could not discuss these two aspects since such information were not assessed in the pathological diagnosis during 2003 and 2011 when the included patients received treatment in our cancer center. A future prospective and randomized clinical trial should be initiated to further answer the questions. In addition, the small sample size also affected the statistical test power. The collaboration among multiple cancer centers to enroll more cases should be done in future studies.

In summary, in a retrospective single-center attended cohort study we investigated the oncological effect of NCT on patients with OSCC and its influence on the following surgery. NCT plus surgery could not improve survival compared with upfront surgery. Although our results suggested NCT could modify the surgical extent and would not affect the surgical margins, the conclusion should be made cautiously. A future randomized clinical trial was needed to further answer the question.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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