Salvage Surgery for Patients With Residual Diseases After Improper or Insufficient Treatment of Oral Squamous Cell Carcinoma: Can We Rectify These Mistakes?

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Research article

Keywords: Salvage surgery, residual, rapid recurrent, positive margin, management

Posted Date: December 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-121119/v1

Version of Record: A version of this preprint was published at BMC Cancer on July 31st, 2021. See the published version at https://doi.org/10.1186/s12885-021-08600-2.

Abstract

Background:

Patterns of failure after treatment of oral and squamous cell carcinomas (OSCC) are diversified, with recurrences being one of the common causes. A special group of patients are sometimes encountered in the outpatient clinic for improper or insufficient initial treatment with reports of positive margins, implying residual diseases. The question of whether these patients can be surgically salvaged remain unanswered.

Methods:

A retrospective study was performed between January 2013 and December 2017 for patients with residual or rapid recurrent (within 3 months) OSCCs, who received salvage surgeries in our institution. The patients with residual OSCCs were those with microscopic or macroscopic positive surgical margins, while those with rapid recurrent OSCCs were those with close or negative margins, but unabated painful symptoms right after treatment. Both clinicopathological and prognostic variables were analyzed. The focus was also directed towards lessons for possible initial mistakes, resulting in these residual diseases.

Results:

Of 103 patients, 68 (66%) were men, with mean age of 56.3 years. The overall survival reached 60.2%. Regarding the primary OSCC status, most of our patients (n=75, 72.8%) were diagnosed with T2-3 stages. Besides, most patients were found with macroscopic residual diseases (52.4%) before our salvage surgery. The sizes of the residual OSCCs were generally under 4 cm (87.3%) with minimally residual in 21 (20.4%). Among all the variables, primary T stage (p=0.003), and residual lesion size (p<0.001) were significantly associated with the prognosis in multivariate analysis. Though the causes for the initial surgical failure were multifactorial, most were stemmed from poor planning and unstandardized execution.

Conclusions:

Cases with residual OSCCs were mostly due to mistakes which could have been avoided under well-round treatment plans and careful surgical practice. Salvage surgery for cases with smaller residual OSCCs is still feasible with acceptable outcomes.

Background:

Primary standard of care for oral squamous cell carcinoma (OSCC) patients remains surgical, with or without adjuvant therapies[1]. Though advancements of techniques and regimens have resulted in cure in about 60% of patients, failure of such treatment is still common[1, 2]. Most of authors tended to owe the patterns of treatment failures to recurrences or/and distant metastases[3, 4]. However, the vague definition of “recurrences” in most reports have confused two groups of patients, residual and recurrent, who were drastically distinct in terms of clinical characteristics and prognoses, as patients with residual diseases

were mostly those with initial positive margins[5]. Even within the so-called “recurrent” patients, some were however actually suffered from unabating painful symptoms right after initial resections, indicative of vastly inappropriate treatment, though with questionable prior reports of “negative” margins[6, 7]. From our perspective, despite the initial curative intent, most cases with positive margins or persistent symptoms (confirmed by biopsies) should be regarded as “residual”, rather than “recurrent” OSCCs, on account of their vastly insufficient prior treatment. Besides, some of them will seek possible immediate retreatment or consultation in other larger regional or national cancer centers, especially for chances of surgical re-resections. However, there were limited data or evidences available describing the treatment for such subgroups of patients. Thus, we try to share our experiences highlighting both causes in these OSCC patients with residual (persistent) diseases. The other aim of our study was to investigate whether immediate salvage surgery (SS)-based efforts can rectify the mistakes of undertreatment in these patients.

Methods:

We performed a retrospective chart review of all the patients who received SS for recurrent OSCCs from January 2013 to December 2017 in our institution, a national referral center for head and neck cancer treatment. The collection and analyses of the data was approved by the institution's ethics committee. The reference number is SH9H-2020-T300-1.

The detailed inclusion (eligibility) criteria were as follows: 1) patients who had the histories of surgical treatment for primary OSCCs in other institutions; 2) those with residual diseases confirmed by reports for positive margins, or those with negative margins but encountering rapid recurrences within 3 months; 3) patients consent to immediate SS and received re-treatment within 3 months after previous treatment; 4) those with postoperative (after SS) pathological confirmation of residual OSCCs. Patients included should meet all the above inclusion criteria. Besides, the exclusion criteria were as follows: 1) patients who received non-surgical treatment only; 2) those with distant metastases; 3) those with unknown information regarding primary treatment.

Demographic data, medical histories, comorbidities, OSCC characteristics, and pretreatment status were collected. Emphasis was given towards the patterns of the initial treatment, with possible causes for previous undertreatment failures. Clinical stages regarding the primary OSCCs were based on American Joint Committee on Cancer (AJCC), 8th edition[8]. Besides, pathological information about depth of invasion (DOI) and extra-nodal extension (ENE) were sent and reviewed again by the Department of Pathology for those receiving primary treatment before 2018. Other clinicopathological parameters regarding the number of positive margins, sizes of residual lesions, midline involvement, differentiation, neurovascular invasion, mandibular/maxillary bone invasions were also collected.

The possible causes for initial surgical failure were analyzed with a focus on the referral reports. Communication records (with the initial treatment clinics), and the patients’ counseling records were also

found in the outpatient clinical database. Specific causes were summarized after reviewing the information.

Based on the varied admission status to our institution, all the included patients were firstly classified into three categories: patients with microscopic residual diseases (MiRDs); with macroscopic residual diseases (MaRDs) or with rapid recurrent diseases (RRDs). MiRDs were defined as those with reports of initial positive margins, and suspected residual diseases via physical examination (palpable) and imaging (invisible or indeterminant), while MaRDs were those with both gross (palpable and visible) residual diseases and initial positive margins, while RRDs were defined as those with initial negative margins but visible residual diseases right after prior operations (< 3 months). Apart from that, as far as the involved subsites were concerned, the studied cohort was further divided into three groups: with local residual, regional (cervical) residual, and both locoregional residual diseases. In consideration of the distinct residual tumor sizes, the extent of SS was tentatively graded according to the re-resections and reconstructions: 1 for simple re-resections, or simple re-neck dissections followed by direct wound closure or local flaps coverage; 2 for radical re-resections with reconstructions with pedicled pectoralis major myocutaneous flaps (PMMF) or free flaps; 3 for SS involving craniofacial resection (skull base), carotid artery resection, total glossectomy, total maxillectomy with orbital exenteration, or hemi-mandibulectomy, with free-flap reconstructive procedures.

In order to analyze the efficacy of our immediate salvage treatment, these patients were also classified into two groups based on different presurgical treatment: patients received upfront SS (SS group); and those underwent adjuvant treatment regimens first, followed by SS (AT-SS group). The SS complications were recorded as well. In addition, various adjuvant treatment modalities were applied to these patients. For sake of statistical analysis, the postoperative adjuvant treatment (after SS) was further summarized into five categories: none, radiotherapy, radio-chemotherapies, radio-chemotherapy with targeted therapy, and radio-chemotherapy without targeted therapies. None of the patients received simple postoperative chemotherapy with/without targeted therapies. The targeted drugs included epithelial growth factor receptor inhibitor (Nimotuzumab or Cetuximab), and vascular endothelial growth factor receptor inhibitor (Apatinib). However, due to the unavailability of PD-1 related pembrolizumab at that time, immunotherapies were not applied in any of these patients.

Overall survival (OS) time was calculated as the time from the start of SS to death/last outpatient visit in months. Salvage outcomes were recorded and compared between these patients with residual OSCCs. The Chi-square test and Fisher exact test were used to compare categorical variables. Univariate log-tank test was adopted to analyze survival time-dependent variables. Subsequently, Cox regression analysis was carried out on the variables that achieved univariate statistical significance. All statistical analyses were conducted via SPSS 21 for Windows (IBM, Chicago, Illinois).

Results:

Demographic information

During the 5-year interval (from 2013 to 2017), a total number of 1761 patients with recurrent malignancies had received SS in our institution, according to the chart database. Within these patients, 103 (5.84%) met our inclusion criteria of patients with “residual OSCCs”. Of these, 68 (66%) were men and the rest were women (n = 35, 34%); The average age reached 56.3 years, of whom 42.7% were smokers. Most patients (n = 36, 35.0%) were with initial diagnoses of tongue cancers, followed by buccal (20.4%), lower gingival (20.4%) and floor-of-mouth (20.4%). The mean follow-up reached 31.1 months (range, 4–65 months). The detailed demographics were summarized in Table 1.

Table 1
Demographic and clinicopathological characteristics for initial treatment

Characteristics	Number (%)	Overall survival (%)	*p*(Log-rank)
Sex			
Male	68(66.0)	67.6	0.046
Female	35(34.0)	48.6	
Age			
< 60	60(58.3)	60.0	0.744
≥ 60	43(41.7)	60.0	
Comorbidity			
Cardiovascular diseases	20(19.4)	70.0	0.459
Diabetes	7(6.8)	57.1	
Others	4(3.9)	100.0	
Combinations	12(11.7)	66.7	
None	60(58.3)	55.0	
Site of primary OSCC			
Tongue	36(35.0)	61.1	0.600
Floor of mouth	13(12.6)	76.9	
Bucca	21(20.4)	70.0	
Lower gingiva	21(20.4)	47.6	
Upper gingiva	8(7.8)	62.5	
Hard palate	4(3.9)	50.0	
Primary T stage			
T1	2(2.0)	100.0	0.011
T2	27(26.2)	74.1	
T3	48(46.6)	64.6	
T4	26(25.2)	38.5	
Primary N grade			
N0	64(62.1)	62.5	0.344
N1	19(18.4)	68.4	

Characteristics	Number (%)	Overall survival (%)	*p*(Log-rank)
N2	10(9.7)	40.0	
N3	10(9.7)	60.0	
Primary stage			
Early stage	23(22.3)	65.2	0.680
Late stage	80(77.7)	60.0	
DOI of primary OSCC			
> 10 mm	45(43.7)	68.9	0.092
≤ 10 mm	58(56.3)	55.2	
ENE of primary OSCC			
With ENE	10(9.7)	61.3	0.757
Without ENE	93(90.3)	60.0	
Primary histological grade			
Highly differentiated	16(15.5)	68.8	0.747
Moderately differentiated	65(63.1)	60.0	
Poorly differentiated	22(21.4)	59.1	
Neck dissection for primary OSCC			
Bilateral neck dissections	8(7.8)	65.9	0.116
Ipsilateral neck dissection	51(49.5)	60.8	
None	44(42.7)	37.5	
Margin status after primary sugery			
Positive	80(77.7)	60.0	0.711
Negative	23(22.3)	65.2	
Number of positive margins*			
1	54(67.5)	63.0	0.711
2	25(31.3)	52.0	
3	1(1.3)	100.0	
Positive deep margin*			
Yes	37(46.3)	56.8	0.714

Characteristics	Number (%)	Overall survival (%)	*p*(Log-rank)
No	43(53.8)	62.8	
Primary reconstruction			
Primary closure	18(17.5)	66.7	0.117
Local flap or skin graft	57(55.3)	66.7	
Free flap and PMMF	28(27.2)	46.4	
Neoadjuvant therapy for primary OSCC			
Yes	14(13.6)	35.7	0.006
No	89(86.4)	65.2	
Ceased adjuvant therapy after primary surgery			
No adjuvant therapy	98(95.1)	60.2	0.432
Ceased adjuvant therapy	5(4.9)	80.0	
*: Only patients with positive margins were included.			

Initial treatment and possible causes for failures

With regards to the primary disease status, most patients (n = 74, 71.8%) in our series were diagnosed with primary T3-T4 stages. Within these, DOI > 10 mm was confirmed in 45 (43.7%) patients after pathological review, resulting in the increased 21 (20.4%) cases of T3 stages. The patterns for primary N stages were different, with merely 20 (19.4%) patients with higher nodal metastasis grades (N2-3). The pathological grades of the primary OSCCs were as follows: highly differentiated grade in 16 (15.5%) cases, and poorly differentiated in 22 (21.4%). Neoadjuvant chemotherapy was applied in 14 (13.6%) patients, while most received upfront primary surgery. As for the extent of the initial surgery, a total number of 59 (57.3%) received ipsilateral or bilateral neck dissections. When comparing the surgical procedures, direct wound closure and local flaps were mostly frequently used for defect coverages (72.8%). The important postoperative reports for surgical margins revealed that 77.7% (n = 80) patients were positive, within whom an astounding number of 53 (51.5%) were without any reports of frozen intraoperative margins according to the referral information. Judging from the initial reports, the primary resections were quite arbitrary, with 26 cases with two or more positive margins. Unfortunately, of these residual OSCC patients, a large proportion (n = 37, 35.9%) were with insufficient deep margins, implying ill-considered surgical decisions or incomplete resections. Within the whole group, 23 (22.3%) patients were with reports of “negative” margins while they still suffered from the persistent symptoms (mostly pain) after prior surgical treatment. A closer inspection of these initial “negative” margins revealed that 14 (13.6%) were suspected for close margins (< 5 mm), while 9 (8.7%) were found with intraoperative re-

resections due to firstly positive-margin reports. All these “negative” margins were later doubted due to the confirmed biopsies prior to SS. The initial radiotherapy was administered to 5 patients, yet all ceased and resort to retreatment in our institution. Thus, most patients in this study were radiation-naïve. (Table 1)

Referral status and initial failure analysis

Within these patients with unsuccessful prior treatment, most (n = 78, 75.7%) were referred by other institutions in the first place, while some were initiated by patients themselves. After communication with all the transfer-applying doctors, most of the referred patients (74, 71.8%) received initial surgical treatment in institutions of low-volume OSCC cases loads (< 50 cases per year), while others were from institutions of high-volume OSCC cases loads. Nineteen (18.4%) patients were with elderly ages over 70, while comorbidities were found in 41.7% (n = 43) of the entire cohort. Interesting, we found insufficient surgical margin information (≤ 3 margins taken/patient) in almost half (45.6%) of the referral reports, indicative of inadequate margin analyses. Besides, the clinical diagnoses were mistaken for other pathologies in 17 (16.5%) patients, while even 23.3% patient received initial operations without confirmations by preoperative biopsies. Within those who received preoperative biopsies, improper delays (> 2 months) between biopsy and surgery were found in 16 patients (15.5%), due either to patients’ or iatrogenic reasons. Interesting, the counselling records with patients revealed that a striking number (n = 41, 39.8%) of patients in this study were reluctant or terrified to receive radical tumor resections with free-flap reconstructions in the initial treatment settings. Besides, from a surgical standpoint, treatment design loopholes were plentiful in these cases, with insufficient margins of depth (35.9%), mismatch between lesion sizes and resection/reconstruction methods (31.1%). Unstandardized operative practices were also suspected for residual lymph nodes found in the cervical basin (n = 24, 23.3%) after initial neck dissections. On the other hand, non-en-bloc (non-continuity) resections were applied in T4 cases (n = 11, 10.7%) involving tongue, floor of mouth, low gingiva, resulting in possible residual lesions in the middle zones. *(*Table 2*)*

Table 2
Referal status and possbile causes for residual OSCCs

Referal status and possbile causes	Number (%)
Referal status	
Institutional referal	78 (75.7)
Patient's decision	25 (24.3)
Primary treatment center	
with low-volume oral cancer cases	74 (71.8)
with high-volume oral cancer cases	29 (28.2)
Surgeon's expertise	
Junior consultant	22 (21.4)
Senior consultant	69 (67.0)
Surgeons of nonrelated specialty	12 (11.7)
Age of patients	
70	84 (81.6)
≥ 70	19 (18.4)
Comorbidities	
Yes	43 (41.7)
No	60 (58.3)
Reports of intraoperative frozen section	
Yes	50 (48.5)
No	53 (51.5)
Report completeness for primary margins	
≤ 3 margins	47 (45.6)
3 margins	56 (54.4)
Clinical stage	
Early stage	23 (22.3)
Late stage	80 (77.7)
Clinical diagnosis before primary surgery	
Correct	86 (83.5)

Referal status and possbile causes	Number (%)
Wrong	17 (16.5)
Biopsy before primary surgery	
Yes	79 (76.7)
No	24 (23.3)
Time Lag between outpatient biopsy to primary admission*	
≤ 2 month	63 (79.8)
> 2 month	16 (20.2)
Patient's initial reluctancy to radical resection/reconstruction	
Yes	41 (39.8)
No	62 (60.2)
Treatment design mistakes[&]	
Flawed access for advanced cases	21 (20.4)
Undertreatment regarding tumor depths	37 (35.9)
Mismatch between imaging sizes and resection methods	32 (31.1)
None of the above	41 (39.8)
Unstandardized operative implementations[&]	
Residual positive lymph node in operated cervical basin	24 (23.3)
Non-enbloc resection for advanced lesions	11 (10.7)
None of the above	78 (75.7)
*: Only patients with biopsies before primary surgeries were included.	
&: These different mistakes might overlap in the primary treatment of the same patients.	

Clinicopathological data for residual OSCCs

According to the previously mentioned classification, most patients in our study were in the MaRD group. In terms of size, most of the residual OSCCs (n = 69, 67.0%) were not larger than 4 cm, suggestive of the curable local conditions. Within these, 45.7% were with gross (> 2 cm) residual lesions. Upper and lower vital-structure (skull base, orbit, carotid artery) involvement were found in approximately 13% of the cases, for whom SS was even more challenging. After SS, pathological differentiation upgrades were

found in 23 (22.3%) patients with residual OSCCs. Besides, neurovascular invasions were confirmed in 19.4% of the cases. As for the salvage treatment, eighty-five (82.5%) cases received upfront SS, while others (n = 18, 17.5%) were in the AT-SS group. The extent of SS was more extensive than the initial treatment, with 78.5% (n = 84) receiving radical resections and flap reconstructions. Within these patients, complicated wide-excision surgery, such as craniofacial skull base surgery, total glossectomy, total maxillectomy or hemi-glossectomy were not rare (25.2%). Despite our SS, post-salvage margin reports still revealed positive margins in 4 (3.9%) cases, of whom most were with larger (> 4 cm) residual OSCCs, or lesions, extending near or through vital structures. In addition, 37 patients experienced complications in postoperative settings. Most were minor wound infections or lung infections. In addition to SS, adjuvant therapies based on radiotherapy or radio-chemotherapy, were offered to most cases (n = 84, 81.6%), while targeted therapies were to 17 (16.5%) (Table 3*).*

Table 3
Clinicopathologcial information about residual OSCCs

Characteristics	n (%)	OS (%)	*p*(Log-rank)
Residual subgroup			
MiRD group	26(25.2)	84.6	0.005
MaRD group	54(52.4)	48.1	
RRD group	23(22.3)	65.2	
Residual OSCC location			
Local	79(76.7)	60.8	0.950
Regional	12(11.7)	66.7	
Locoregional	12(11.7)	58.3	
Size of rOSCC*			
Minimal residual	21(20.4)	81.0	< 0.001
≤ 2 cm	35(34.0)	71.4	
2-4cm	34(33.0)	55.9	
> 4 cm	13(12.7)	15.4	
rOSCC involving vital structures#			
Yes	13(12.6)	38.5	0.049
No	90(87.4)	64.4	
Differentiation for rOSCC			
Highly differentiated	9(8.7)	66.7	0.857
Moderately differentiated	60(58.3)	61.7	
Poorly differentiated	34(33.0)	58.8	
Pathological upggrade for rOSCC			
Yes	23(22.3)	69.6	0.583
No	80(77.7)	58.8	
Neurovascular invasion for rOSCC			
Yes	20(19.4)	70.0	0.583
No	83(80.6)	59.0	

Characteristics	n (%)	OS (%)	*p*(Log-rank)
Bone invasion for rOSCC			
Yes	31(30.1)	45.2	0.023
No	72(70.0)	70.0	
Margin status after salvage surgery			
Positive	4(3.9)	0.0	< 0.001
Negative	99(96.1)	63.6	
Complication after salvage surgery			
Yes	37(35.9)	56.8	0.488
No	66(64.1)	63.6	
Detailed complications			
Wound dehiscense or infection	14(37.8)	57.1	0.436
Flap crisis or failure	4(10.8)	25.0	
Lung infection	12(32.4)	58.3	
Chyle leak	1(2.7)	100.0	
Deep venous thrombosis	2(5.4)	100.0	
Hematoma	1(2.7)	100.0	
Others	3(8.1)	33.3	
Salvage treatment combinations			
Upfront salvage surgery	85(82.5)	64.7	0.033
Adjuvant therapy followed by salvage surgery	18(17.5)	44.4	
Salvage resection and reconstruction			
Simple resection with direct closure or local flaps	19(18.4)	89.5	0.001
Radical resection with free flap or PMMF coverage	58(56.3)	62.1	
Craniofacial surgery, total glossectomy, etc	26(25.2)	38.5	
Adjuvant therapy			
Radiotherapy	43(51.2)	58.1	0.156
Radiochemotherapy	25(29.8)	60.0	
Radiotherapy with targeted therapy	10(11.9)	50.0	

Characteristics	n (%)	OS (%)	*p*(Log-rank)
Radiochemotherapy with targeted therapy	6(7.1)	33.3	
None	19(18.4)	84.2	
* Sizes of residual OSCCs (rOSCC) were determined by pathological reports, with minimal residual lesions signifying lesions smaller than 1 cm.			
#: Vital structures: Carotid artery, skull base or higher, glottic, hypopharynx, larynx			

Table 4
Correlations between clinicopathological characteristics between initial and residual OSCCs

Initial treatment	Residual retreatment	p values
Primary T stage	**Residual subgroup**	**< 0.001**
	Size of residual OSCC	**< 0.001**
	rOSCC involving vital structures	**0.017**
	Salvage treatment combinations	**< 0.001**
	Salvage resection and reconstruction	**0.001**
Neoadjuvant therapy for primary OSCC	**Size of residual OSCC**	**0.024**
	Salvage treatment combinations	**0.002**
	Salvage resection and reconstruction	**0.011**

The correlation between the parameters regarding initial treatment and residual retreatment were analyzed. Both primary T stage ($p < 0.001$) and neoadjuvant therapy ($p = 0.024$) were found to be related to residual lesion size. Primary T stage was also correlated with the residual subgroup ($p < 0.001$), and vital-structure involvement ($0 = 0.017$).

Survival outcomes and statistical analyses

The OS rate reached 60.2%, with 41 death within the whole group. When it comes to the specific death causes, locoregional re-recurrences were found in 26 (25.2%) cases, while both recurrences and distant metastases in 11 (10.7%), representing the two major reasons for our salvage failures. The univariate log-rank analyses of the initial treatment data revealed that sex ($p = 0.046$), primary T stage ($p = 0.011$) and neoadjuvant therapies (0.006) were related to the patients' prognosis. As for the residual OSCC data, the univariate analyses showed significances in residual subgroups ($p = 0.005$), size of the residual OSCC ($p < 0.001$), vital-structure involvement ($p = 0.049$), bone invasion ($p = 0.023$), salvage margin status ($P < 0.001$), salvage treatment combinations (0.033) and salvage resection and reconstruction extent (0.001).

Among all the variables, both primary T stage (p = 0.003), and residual lesion size (p < 0.001) were significantly associated with OS, based on the final Cox multivariate analysis (Table 5, Fig. 1).

Table 5
Cox multivariate analysis of SS for patients with residual OSCCs

Parameter	*p*	HR#	95.0% CI#	
Primary T stage	0.003	1.96	1.262	3.044
Size of residual OSCC*	< 0.001			
≤ 2 cm	< 0.001	0.112	0.035	0.357
2-4cm	< 0.001	0.201	0.084	0.480
> 4 cm	0.006	0.328	0.149	0.723
#HR = Hazard Ratio, CI = Confidence Interval				
*:The analyses was based on the reference of minimal-residual group.				

Discussion:

It is well known that the best opportunity to cure patients with OSCC is through the delivery of fast and appropriate therapy at first presentations[8–9]. Theoretically speaking, management of “recurrence” after prior treatment is a challenging clinical situation, with decreased chances of cure by retreatment[10]. Although there is no standard criteria or consensus of a “true recurrent” OSCC, most still consider “recurrences” as those with similar pathological profiling, involving nearby anatomic structures (< 3 cm) and within 3 years of follow-up[11]. In literature, such “recurrences” were only divided by years, as either rapid or late recurrences, irrespective of detailed primary treatment[10–12]. As far as we are concerned, initial treatment, primary surgical margin and postsurgical symptom (pain) should all be taken into consideration when differentiating true “recurrent” and “residual” OSCCs, as some “recurrences” were in fact residual lesions (without intermittent remission of symptoms)[13]. These OSCCs become residual due more to improper initial treatment or insufficient resections, rather than to oncological aggressiveness of OSCCs. Determining the optimal retreatment regimens for this special group is very important, as most patients are extremely anxious about the likelihood of rapid and curative salvage re-resections[14]. According to the referral/admission report, the report of positive margins, along with the unrelieved painful symptoms, always encroached on the retreatment confidence in the primary treatment centers, given the fact that a high proportion (24.3%) of referrals were requested by patients. As occasionally encountered with these referrals, we tried to answer the question of whether these patients with residual OSCCs could still be rescued with SS-based treatment, as controversy for such decisions still exists.

Such residual OSCC problems were caused by a lot of factors, which however has long been under-evaluated. To a large extent, initial (primary) treatment status will negatively influence the survival

outcomes[16]. Firstly, the factors of surgeons should not be downplayed. According to the referral reports and patients' statements, the initial surgical treatment was carried out in some patients with unproven preoperative biopsies, which violated the principles of National Comprehensive Cancer Network (NCCN) guidelines[17]. Such condition was mostly due to false biopsy practice or lack of experiences for OSCC diagnosis. Besides, sometimes the variety of clinical presentations of OSCC and other premalignant oral lesions will also confuse the clinical diagnosis[18]. From a baseline diagnostic perspective, single or multiple incisional biopsies are required for large and non-homogenous lesions to confirm the OSCC diagnosis preoperatively[18]. The other mistake was the surgical completeness. Mismatch between primary OSCC stages and resection/reconstructive methods were abundant in our series, as some locally advanced lesions (n = 32, 31.3%) were even resected and reconstructed with direct closure or local flaps. Thus, the radicality of initial treatment was seriously questioned in these cases. In addition, a fairly large number of the cases in our study were with initial positive deep margins, implying possible flawed intraoperative resection regarding the tumor depth, which will finally compromise the treatment efficacies[20, 21]. Due to the terrible margin status in most patients, we advocate that en-bloc, or even compartment surgeries should be strongly recommended to ensure margin safety, particularly for adequate deep margins in advanced primary cases[23, 24]. Interestingly, even in some cases with primary early-stage OSCCs, residual lesions were still found in the tumor basins. We figured that such iatrogenic mistakes, which could have been avoided, were mostly due to unprepared preoperative surgical plans. For example, for cases with tongue cancers, the para-glossal resections should not be overly conversed for lingering fear of oro-cervical communications. The removal of sublingual gland and floor of mouth mucosa should also be advocated for a clear middle-zone eradication[22–24]. For cases with buccal cancers, especially those in the anteromedial buccal subsites, thorough-and-thorough resections should be attempted despite possible cosmetic disfigurement. For retromolar and lower buccal lesions, the resections of medial, sometimes lateral pterygoid muscles, marginal medial mandibulectomy should always be highlighted in those with clinically presentations of seemingly "early-stage" diseases, with true invasive fronts regarding the tumor depths[25–27]. Anatomically speaking, these parapharyngeal structures are adjacent, or in direct connection with the oral epithelial tissues, where improper surgical practice will result in positive margins[26]. Considering the treatment outcomes of these residual lesions, it is better to "err on the safe side" for extending the margins a bit wider, and to prepare intraoperative flap reconstructions, especially for some clinically T2-3 cases[26, 27]. Besides, the existence of cervical residual OSCCs were, in our opinion, partly due to unstandardized or improper resections or neck dissections, and to higher primary N grades which had also been cited in other studies as the reasons for regional (cervical) recurrences after neck dissections[9, 28]. We consent to the recent Clinical Practice Guideline issued by American Society of Clinical Oncology for establishing preliminary recommendations on the preliminary criteria of a high-quality neck dissection[9]. The anatomic hallmarks, levels and lest number of nodal specimens should also be emphasized for the best practice of surgical care for OSCC patients.

Apart from the surgical problems, as reflected in Table 2, other clinical factors should also be cautiously evaluated for avoiding treatment malpractice. Firstly, as is reflected in our series, 41.7% of the cases were

with comorbidities, which might cause hesitations of aggressive surgical treatment from the patients' and doctors' perspectives[29]. Besides, the competencies of surgeons for such OSCC treatment should be assessed[30], as 33.1% of the patients in our study received their initial treatment from junior consultants, or even surgeons from other non-relating specialties. Besides, patients who received surgical treatment from low-volume peripheral institutions tend to have improper or low-quality treatment practice in our series, with more chances of positive margins and lower likelihood of providing care adherent to guidelines[31–32]. However, such view was refuted by Eskander for conflicting evidence comparing the quality of care between high- and low-volume institutions[33]. For us, the ample experiences of treating OSCC on a regular basis made difference between different institutions and surgeons. In addition, the adverse survival relationships of "delays between biopsies and treatment" was consistent with the reports of others[34]. Due to such varied negligence in primary treatment, we call for strictly adhering to the treatment and diagnosis guidelines otherwise it may cause tremendous disaster to the patients.

For the treatment of resectable residual diseases, there were still unsettled controversies about the role and outcomes of SS, with vastly conflicting survival outcomes ranging from 8.3–62.5%[6, 10, 36, 37]. Most of these studies were with both residual and recurrent OSCC cases, which were further complicated by a higher proportion of patients with histories of prior radio- or radio-chemotherapies[6, 37]. We came up with the first report for the outcomes of immediate SS-based treatment against residual OSCCs, who were mostly radiation-naive. The answer of salvage likelihood for residual OSCCs was partially answered in our study, as the survival outcomes diversified among these patients. According to us, careful case selections for immediate SS should be emphasized based on both the initial and residual status. In the current study, patients with both smaller primary and residual OSCC sizes were mostly salvageable under a sound retreatment. However, for cases with larger residual disease burdens, the prognosis was generally unfavorable with a meager survival of 15.4%. The involvement of vital structures in residual OSCCs were also found to decrease the likelihood of rescue. As for the treatment designs, we found a slight advantage of survival for the SS group over AT-SS group. A stronger association was also found for the salvage resection and reconstruction extent, as most patients with wide margin re-resections and free-flap (including PMMF) reconstructions enjoyed better survival outcomes. Adjuvant radio- or radio-chemotherapy following SS should be considered in patients with residual OSCCs for a 10–20% survival advantage, which was also reported in other studies for recurrent OSCCs[38, 39]. As for other treatment combinations, the effects of targeted (EGFR or VEGF-based) therapies fell short of expectations as the trends of treatment outcomes reversed despite such added treatment regimens. We owed this phenomenon to both the treatment toxicities, and to the more advanced disease status of those who were inclined to receive such combinations. As far as we are concerned, routine postoperative radiotherapy or radio-chemotherapy was able to reach a similar, or even better outcome without the supplement of molecular targeted therapies, judging from our statistics.

Some limitations were inherent in the present study. Firstly, our results were obtained in a retrospective cohort in a single institution. Secondly, the treatment benefits for advanced residual cases were unable to summarize due to the small number in this investigation. Most patients were also irradiation-naïve in the

primary treatment. In addition, the case selection for curative SS were quite subjective. Lastly, the effects of immunotherapies were elusive given the absence of such treatment at that time.

Conclusions:

When encountered with primary OSCC cases, a well-round, evidence-based surgical plan, together with an able surgical expertise, is mandatory for the ultimate treatment success. Cases with residual OSCCs were mostly due to mistakes which could have been avoided if the guidelines and practice codes were strictly followed. SS for cases with both smaller residual radiation-naïve OSCCs is still feasible with acceptable outcomes, when carefully designed and performed.

Abbreviations:

OSCC: oral squamous cell carcinoma;

SS: salvage surgery;

AJCC: American Joint Committee on Cancer;

DOI: depth of invasion;

ENE: extra-nodal extension;

MiRDs: microscopic residual diseases;

MaRDs: macroscopic residual diseases;

RRDs: rapid recurrent diseases;

PMMF: pectoralis major myocutaneous flap;

OS: overall survival;

NCCN: National Comprehensive Cancer Network;

AT-SS: adjuvant treatment regimens first, followed by SS

Declarations:

Ethics approval and consent to participate

Ethical consent was issued by the Independent Ethical Committee of Shanghai 9th People's Hospital, Shanghai Jiao Tong University School of Medicine. The committee reference number is SH9H-2020-T300-1.

Consent for publication

Permission for publication was obtained from the participants in this study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by Science and Technology Commission of Shanghai Municipality, Grant Number: 19ZR1430000; Hospital Innovation Project, Grant Number: CK2019004; Hospital Cross-Multidisciplinary Project, Grant Number: JYJC201911 for clinical data acquirement, statistical analysis fees and pathological review of the patients' samples.

Authors' contributions

YH and XT wrote and revised the manuscript. ZL and SS collected and present their cases, wrote the figure lengths and representative case descriptions. WG collected the data and revised the manuscript in 9th People's Hospital. XL and CM designed the studies and gave the idea of the presentations. All authors have read and approved the manuscript.

Acknowledgements

We gave our sincere gratitude to Prof. Chenping Zhang for his help and guide during the revision of the manuscript.

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Figures

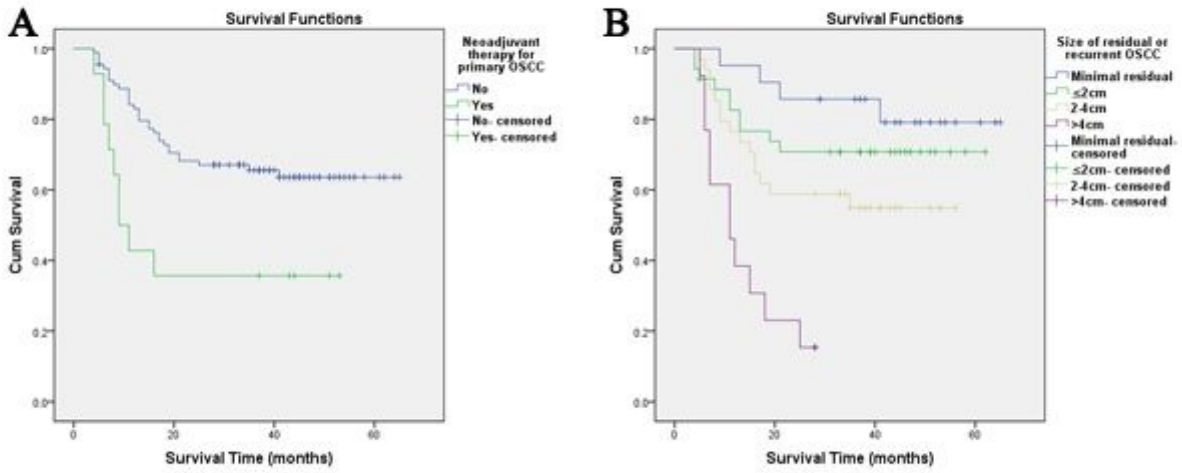

Figure 1

The Kaplan-Meier curves for the significant variables in Cox multivariate analyses. A. Primary T stage; B. Residual OSCC size;

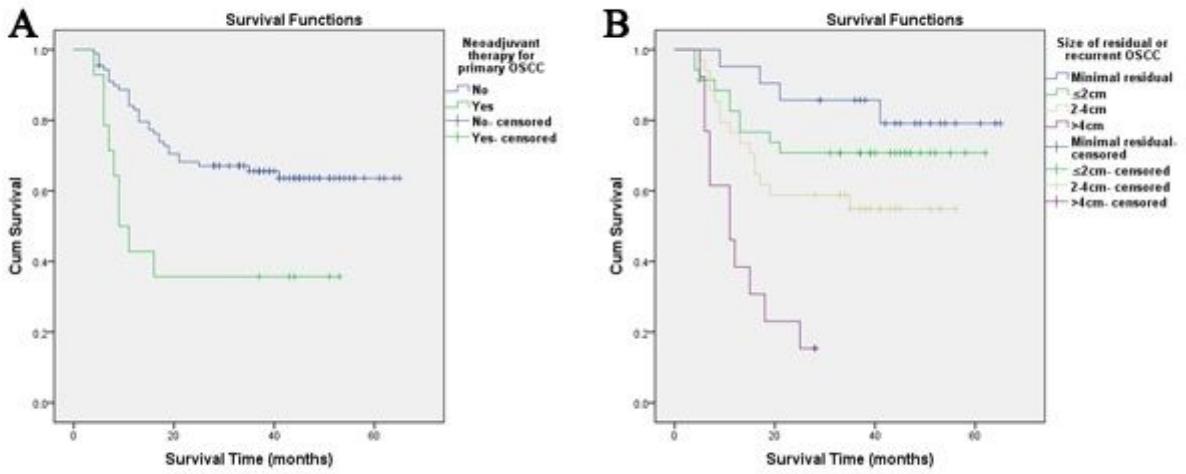

Figure 1

The Kaplan-Meier curves for the significant variables in Cox multivariate analyses. A. Primary T stage; B. Residual OSCC size;

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