

# Quality of life after salvage surgery for extensively recurrent head and neck cancer patients: a prospective, observational, real-world study

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## Research Article

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# Abstract

## Purpose

Multiple studies on salvage surgery (SS) implied the efficacy but the estimate of quality of life (QOL) after SS was poorly analyzed. Our study aimed to examine the quality of life before and after salvage surgery using the validated instruments QLQ-H&N35 and UW-QOL and investigate the value of salvage surgery by quantifying survival outcomes.

## Materials and methods

Among 21 patients, preoperative and postoperative QOL were accessed using QLQ-H&N35 and UW-QOL questionnaire. Patients' demographic characteristics, history of treatment, recurrent tumor characteristics, salvage surgery details and follow-up date were abstracted from our prospective database. Statistical analysis methods included Wilcoxon signed-rank test, descriptive analysis and Kaplan-Meier method.

## Results

The overall quality of life was significantly improved after salvage surgery. Pain was significantly relieved whilst diminished functions were hinted with significant differences in UW-QOL domains swallowing, chewing, speech, shoulder, taste, saliva and in QLQ-H&N35 domains swallowing, speech, social eating, senses, dry mouth, sticky saliva as  $p \leq 0.05$ . The median disease-free survival of whole 21 patients was 5 months (range 0-73) and the median overall survival was 13 months (range 1-73).

## Conclusions

The quality of life after salvage surgery for extensively recurrent head and neck cancer is acceptable. Despite the dysfunctions such as dysphagia and dry mouth, it does relieve the pain and improve the short-term overall QOL of patients. Further studies on quality of life before and after salvage surgery in HNSCC are obviously needed. In the future, postoperative functional recovery training also needs attention during follow up.

## Introduction

The morbidity and mortality of head and neck cancers increased gradually, with over 830 000 new cases and nearly 430 000 deaths globally in 2018.[1] In head and neck region, squamous cell carcinomas (HNSCC) takes a proportion of more than 90%[2] and surgery with adjuvant chemoradiotherapy is the most common treatment utilized in head and neck malignant tumors.[3, 4]. Nevertheless, recurrence is still inescapable with rate of 25%-50%,[5] especially for advanced stage cancer (Stage III or IV).[6] Patients with recurrence are faced with less options[7]. The complications caused by previous radiotherapy and

chemotherapy will also have adverse effect on the therapy.[8–10] In addition, resection of widely spread tumors in head and neck region always leads to appearance changing, dysfunction of swallowing, chewing and others, which profoundly impact their quality of life (QOL). Accordingly, extensively recurrent head and neck cancers raise the treatment challenges both in therapy selection and implementation for surgical team.

The term “salvage surgery” (SS) was firstly came up with in 1965, describing surgical treatment after failure of radiotherapy. It is currently identified as a final attempt for residual and recurrent tumors after definitive treatment, including surgical treatment.[11] Multiple studies on SS implied the efficacy[12] with five-year overall survival(OS) and disease-free survival(DFS) rates of 42% and 47% respectively and it has been advocated as the last curative option for recurrent advanced head and neck cancer[13–15]. Although the oncological outcomes of SS showed a substantial improvement, the estimate of quality of life before and after salvage surgery was poorly analyzed. The European Organization for Research and Treatment of Cancer (EORTC) questionnaire and University of Washington Quality of Life (UW-QOL) questionnaire were two most frequently used questionnaires globally measuring QOL of patients with head and neck cancer.[16]

In this study, we tried to examine the quality of life before and after salvage surgery for patients with extensively recurrent head and neck cancer, using the validated instruments QLQ-H&N35 and UW-QOL. A secondary aim is to investigate the value of salvage surgery by quantifying survival outcomes.

## **Materials And Methods**

### **Study sample**

The data of this study originated from POROMS, a Prospective, Observational, Real-world Oral Malignant Tumors Study (clinicaltrials.gov identifier: NCT02395367). This database was established in January 1, 2015, based on the department of oral maxillofacial head and neck oncology, Beijing Stomatological Hospital. It covered demographic and clinical characteristics, medical history, postoperative complications and pre- and post- treatment QOL, etc. In this study, the initial study sample included all treated patients with oncologic malignancy from January 1, 2015 to January 31, 2021. Amidst the mentioned group, we selected eligible patients using the following criteria: (1) patients received resection surgery plus reconstruction with latissimus dorsi flaps or pectoralis major myocutaneous flaps; (2) patients with a tumor recurred more than once (including locoregional recurrence and secondary primary tumor); (3) patients with a tumor invading vital structures (internal carotid artery, skull base, pterygoid plate, masticatory space, parapharyngeal space and orbit); (4) patients provided an informed consent. Patients who lost to follow up and refused to participate were excluded from study. (Figure.1) This study was approved by the Beijing Stomatological Hospital ethics committee and conducted with the informed consent of patients.

### **Instruments**

Pre- and corresponding post- quality of life were measured using QLQ-H&N35 (version 3.0) and UW-QOL (version 4.0). EORTC Questionnaires has been well accepted and widely used to evaluate the quality of life of cancer patients.[17–19] It contains a general questionnaire, QLQ-Core-30 and a specific module, QLQ-H&N35, which evaluates the common areas and specific parts of cancer patients, respectively. QLQ-H&N35 is composed of 7 multi-item scales assessing pain, problems with swallowing, senses (taste and smell), speech, social eating, social contact and sexuality, and 11 single items assessing problems with teeth, opening the mouth, dry mouth, sticky saliva, coughing, feeling ill, as well as use of analgesics, nutritional supplements, feeding tube, weight gain and weight loss. The raw dates were scored on a four-point Likert scale (“not at all,” “a little,” “quite a bit,” “very much”), whereas the last five items were in form of yes/no. The scales scores range from 0 to 100, with higher scores suggested severer symptomatology or problems.[17]

Another questionnaire with the same application is UW-QOL questionnaire, which has been come up with by Hassan and Weymuller[20] in 1993. It consists of 12 single question domains, which contains physical function domains with chewing, speech, swallowing, taste, saliva, appearance, and social function domains with anxiety, mood, pain, activity, recreation, shoulder function.[21] In addition, it also has three global questions, one about how patients feel compared to the month before they developed cancer, one about their health-related quality of life during the last 7days and one about their overall quality of life during the last 7days. For UW-QOL, each domain has 3-6 options scored evenly from 0 to 100, with higher scores implied better quality of life.

## **Date collection and Integrity**

Patients’ demographic characteristics (age, gender), history of treatment (whether underwent radiotherapy, chemotherapy and other treatments), recurrent tumor characteristics (pathologic type, invasion of important structure), salvage surgery details (selection of flaps, results of resection margin) and follow-up date (adjuvant therapy, postoperative complications, DFS and OS) were abstracted from the mentioned database.

All patients registered in database fulfilled postoperative quality of life questionnaires by themselves. Postoperative quality of life questionnaires were completed within 3 months after salvage surgery. Short-term (less than 3 months) follow-up data were collected via subsequent clinical visit. With regard to long-term follow-up date, we encouraged patients return to outpatient clinic for follow-up to ensure the integrity and authenticity of data and telephone follow-up was only used in patients with poor physical condition that cannot come back to the hospital or death.

## **Statistical analyses**

The descriptive analysis was used to identify the sample characteristics. Wilcoxon Signed Rank Test, nonparametric test for two paired samples, was used to detecting differences between pre- and post-QOL. Significance was established as  $p \leq 0.05$ . Overall survival and disease-free survival were calculated by Kaplan-Meier. All statistical analyses were carried out using statistical software program SPSS version 26.0.

## Results

### Sample characteristics

21 patients were eligible for the study with median age of 59 years (range 43-77) at time of surgery. The proportion of men(57%) is slightly higher than that of women (43%). The predominant pathologic type was carcinoma (90%). Patients' characteristics were shown in Table 1.

Table 1  
Demographic and Clinical characteristics

Characteristics	N=21
Age-year	
Median	59
Range	43-77
Gender-n (%)	
Male	12(57)
Female	9(43)
Previous surgery methods-n (%)	
Resection of primary tumor	6(28)
Resection of primary tumor + flap reconstruction	6(28)
Resection of primary tumor + neck dissection	6(28)
Resection of primary tumor +flap reconstruction + neck dissection	3(16)
History of radiotherapy-n (%)	
With	7(33)
Without	14(67)
History of chemotherapy-n (%)	
With	3(14)
Without	18(86)
History of other treatments-n (%)	
With	2(10)
Without	19(90)
Pathologic type-n (%)	
Carcinoma	19(90)
Sarcoma	1(5)
Chordoma	1(5)
Invasion of vital structures- n (%) <sup>a</sup>	

<sup>a</sup> There were 11 patients presented invasion of only one structure, 5 patients got two invaded structures and 5 patients got three.

<b>Characteristics</b>	<b>N=21</b>
Mastication muscles space and parapharyngeal space	20(95)
Skull base	6(29)
Internal carotid artery	2(10)
Pterygoid process	6(29)
Orbit	2(10)
Selection of flaps-n (%)	
Latissimus dorsi flap	18(86)
Pectoralis major musculocutaneous flap	3(14)
Results of salvage surgery-n (%)	
Negative margin	12(57)
Positive margin	6(29)
Positive margin → negative margin	3(14)
Adjuvant therapy-n (%)	
None	8(38)
Radiotherapy	6(28)
Chemotherapy	5(24)
Radiotherapy + Chemotherapy	2(10)
Complications-n (%)	
With	3(14.3)
Maxillofacial edema	2
Flap crisis	2
Bone exposure	1
Pharyngo-cutaneous fistula	1
Without	22(88.0)
<sup>a</sup> There were 11 patients presented invasion of only one structure, 5 patients got two invaded structures and 5 patients got three.	

## Salvage surgery

In terms of the history of prior treatments, patients received resection of primary tumor with or without neck dissection or reconstruction were all 6(29%), and the last 3(14%) patients received resection of primary tumor with both. The number of patients had received radiotherapy or chemotherapy or other treatments were 7(33%), 3(14%), 2(10%), respectively.

Mastication muscles space and parapharyngeal space were the most frequently involved structures with 20(95%) patients, while invasion of skull base involved, internal carotid artery, pterygoid process, orbit were 6(29%), 2(10%), 6(29%), 2(10%), respectively. There were 11 patients presented invasion of only one structure, 5 patients got two invaded structures and 5 patients got three. Most patients chose latissimus dorsi flap(86%). In view of organ preservation and avoiding of fatal complications, approximately 29% patients can't get negative margin, which we called cancer-free resection margin.

The operation process of a typical salvage surgical case is shown in Figure 2. This is a case of a huge recurrent SCC of the maxillofacial region which the lesions involved the oral cavity, skin of the zygomatic face, the outer orbital, sinuses and deep facial area (Figure 2A-C). And radiographic images presented tumor encroached maxillary and mandibular bone, maxillary sinus and orbital floor (Figure 2D-E). The case underwent an extensive resection including maxilla, mandibular ramus, oral buccal mucosa and gingiva, and Zygomatic facial skin and lateral orbital bone wall (Figure 2F). And then, the huge defect was reconstructed with double-skin paddle free latissimus dorsi flaps and titanium mesh implantation of right orbit after all margins were negative (Figure 2G-J). Finally, the case obtained a primary cure, received a satisfactory quality of life, and the tumor was never recurrence followed up for 1 year.

Learned from the follow-up notes, 6(29%) and 5(24%) patients underwent concomitant radiotherapy and chemotherapy, respectively, 2(10%) patients received both and 8(38%) did not receive any adjuvant therapy. The incidence of complications seems low with only 3(14%) patients, manifested as maxillofacial edema, flap crisis, bone exposure and pharyngo-cutaneous fistula.

## **Quality of life measured by UW-QOL**

The scores of UW-QOL before and after salvage surgery were shown in Table 2. The mean scores of overall quality of life prior to salvage surgery was 30.95(95%CI, 25.99-35.92), while that after salvage surgery was 84.52(95%CI, 76.10-92.95). It revealed significant differences ( $p \leq 0.001$ ) with better quality of life after salvage surgery. Among 12 functional domains, the lowest preoperative scores were found in pain(57.14) and lowest postoperative scores were chew(30.95). As for comparative analyses of UW-QOL scores between pre- and post- salvage surgery, significant differences were found in 7 function domains which were pain ( $p=0.021$ ), swallowing ( $p \leq 0.001$ ), chewing ( $p=0.003$ ), speech ( $p=0.004$ ), shoulder ( $p=0.004$ ), taste ( $p \leq 0.001$ ), saliva ( $p=0.011$ ). Among the former items, the domain "pain" achieved better scores which implied the relief after salvage surgery, however, worse scores were found in others hinted the diminished functions. (Figure 3)

Table 2  
Comparison of quality of life between preoperative and postoperative with UW-QOL

UW-QOL	Preoperative	Postoperative	Difference-value*	P-value
	Mean(95%CI)	Mean(95%CI)	Mean(95%CI)	
<b>Functional domains</b>				
Pain	57.14(51.88-62.41)	72.62(63.16-82.08)	15.48(2.77-28.19)	0.021
Appearance	67.86(58.94-76.78)	69.05(62.91-75.18)	1.19(-11.00-13.38)	0.868
Activity	75.00(68.77-81.23)	71.43(57.36-85.50)	-3.57(-18.96-11.82)	0.743
Recreation	76.19(70.53-81.85)	75.00(63.62-86.38)	-1.19(-13.90-11.52)	0.926
Swallowing	80.95(72.33-89.58)	37.14(24.50-49.79)	-43.81(-57.50-30.12)	∞0.001
Chewing	59.52(50.37-68.68)	30.95(17.53-44.37)	-28.57(-43.96-13.18)	0.003
Speech	75.24(63.23-87.25)	40.95(27.61-54.29)	-34.26(-52.53-16.05)	0.004
Shoulder	100.00(100.00-100.00)	73.81(57.43-90.19)	-26.19(-42.70-9.81)	0.004
Taste	100.00(100.00-100.00)	64.29(49.57-79.01)	-35.71(-50.43-20.99)	∞0.001
Saliva	81.43(74.63-88.22)	70.95(65.03-76.87)	-10.47(-17.45-3.50)	0.011
Mood	75.0(69.91-80.09)	63.10(48.87-77.32)	-11.90(-27.84-4.03)	0.136
Anxiety	74.29(69.39-79.18)	70.48(58.31-82.65)	-3.81(-17.20-9.58)	0.227
<b>Composite domains</b>				
Compared to the month before you developed cancer	21.43(17.35-25.51)	82.14(71.26-93.02)	60.71(48.47-72.96)	∞0.001
Health-related quality of life during the past 7 days	30.95(25.99-35.92)	84.52(76.10-92.95)	53.57(43.86-63.28)	∞0.001
Overall quality of life during the past 7 days	30.95(25.99-35.92)	84.52(76.10-92.95)	53.57(43.86-63.28)	∞0.001
*Postoperative value minus preoperative value				

## Quality of life measured by QLQ-H&N35

The results of QLQ-H&N35 were analogous to UW-QOL and listed in Table 3. Pain ( $p \leq 0.001$ ) was significantly relieved whilst dysfunction were found with respect to swallowing ( $p \leq 0.001$ ), speech ( $p=0.006$ ), social eating ( $p=0.006$ ), senses ( $p \leq 0.001$ ). Symptoms of dry mouth and sticky saliva were severer with P-value of 0.011 and 0.046 respectively compared to prior to surgery. Higher frequency of use of nutritional supplements( $p \leq 0.001$ ) and feeding tube( $p=0.046$ ) can also be found, accompany with increase in weight( $p \leq 0.001$ ). (Figure 4)

Table 3

Comparison of quality of life between preoperative and postoperative with EORTC QLQ-H&amp;N35

QLQ-H&N35	Preoperative	Postoperative	Difference-value*	P-value
	Mean(95%CI)	Mean(95%CI)	Mean(95%CI)	
<b>Multi-items scales</b>				
Pain	27.78(22.50-33.05)	7.54(4.88-10.20)	-20.24(-26.65-13.83)	∞0.001
Swallowing	7.54(4.17-10.91)	46.03(32.53-59.53)	38.49(25.77-51.21)	∞0.001
Senses	0.00(0.00-0.00)	18.25(11.09-25.41)	18.25(11.09-25.41)	∞0.001
Speech	15.34(7.27-23.42)	40.21(29.08-51.34)	24.87(9.79-39.95)	0.006
Social eating	17.86(11.71-24.01)	30.95(24.37-37.54)	13.10(4.74-21.46)	0.006
Social contact	14.68(8.90-20.47)	13.33(6.82-19.84)	-1.34(-11.28-8.58)	0.409
Sexuality	0.00(0.00-0.00)	0.00(0.00-0.00)	0.00(0.00-0.00)	1.000
<b>Single-item question</b>				
Teeth	1.59(-1.72-4.90)	1.59(-1.72-4.90)	0.00(-4.80-4.80)	1.000
Opening mouth	38.10(21.98-54.21)	33.33(33.33-33.33)	-4.76(-20.89-11.35)	0.519
Dry mouth	20.63(13.08-28.18)	33.33(25.02-41.64)	12.70(3.75-21.64)	0.011
Sticky saliva	19.05(11.35-26.74)	25.40(18.77-32.02)	6.35(0.24-12.45)	0.046
Coughing	0.00(0.00-0.00)	0.00(0.00-0.00)	0.00(0.00-0.00)	1.000
Felt ill	31.75(25.92-37.58)	38.10(27.06-49.13)	6.35(-2.78-15.48)	0.157
Pain killers	52.38(29.08-75.68)	33.33(11.35-55.32)	-19.05(-58.78-20.69)	0.317
Nutritional supplements	4.76(-5.17-14.70)	100.00(100.00-100.00)	95.24(85.30-105.20)	∞0.001

\*Postoperative value minus preoperative value

QLQ-H&N35	Preoperative	Postoperative	Difference-value*	P-value
	Mean(95%CI)	Mean(95%CI)	Mean(95%CI)	
Feeding tube	0.00(0.00-0.00)	19.04(0.73-37.36)	19.05(0.73-37.36)	0.046
Weight loss	28.58(7.50-49.64)	14.28(-2.04-30.61)	-14.29(-40.38-11.81)	0.257
Weight gain	0.00(0.00-0.00)	61.90(39.25-84.56)	61.90(39.25-84.56)	0.001

\*Postoperative value minus preoperative value

## Survival outcomes

As of January 31, 2021, only 33% of patients were alive. 2-year and 5-year disease-free survival were 24% and 5%, respectively, while 2-year and 5-year overall survival were 52% and 5%, respectively. The median disease-free survival of whole 21 patients was 5 months (range 0-73) and the median overall survival was 13 months (range 1-73). (Figure 5)

## Discussion

In our study, we considered salvage surgery as the treatment for extensively recurrent head and neck cancer. Demonstrated by the questionnaires' outcomes, the QOL of patients has improved after salvage surgery, despite the declines of some functions. The consequences of UW-QOL were in accordance with QLQ-H&N35 in the assessment of physical functions and social functions.

Pain was one of the common symptoms of cancer patients, with no exception in head and neck cancers and it had noticeable impact on QOL. Studies on understanding priorities of patients with HNSCC showed the most concerning of cure, survival and avoiding pain,[22] hinted that it's crucial to improve QOL and enhance their confidence for treatment modalities and life expectancy, aside from prolonging the survival time. Salvage surgery, in the premise of balance with function, can remove the invasion and compression on nerve. Hence, the performance of SS significantly contributed to the relief of severe pain. The compression of tumor also leads to the change of appearance. Better scores were found after SS while with no significant difference. We thought it was caused by the small sample size.

Dysphagia occurred frequently after treatment for HNSCC because of the gross destruction of organs vital for swallowing (e.g. tongue, larynx, mouth floor and pharyngeal wall).[23, 24] The same consequence was found in our study that swallowing decreased significantly with lower scores, in which 17 of 21 patients suffered partly or totally dysphagia and all of them got one or all of these structures involved. The dysfunction of chewing and speech, with significant difference, interrelated with the former anatomical structures as well, combined with masticatory space and jaws. Disorders of these functions provided a powerful push to malnutrition, weight loss and other severe health problem, which adversely

impacted the QOL of carcinoma patients. In other words, the site of tumors was relevant to the QOL. Meanwhile, problems of swallowing and chewing, together with tongue destruction and use of feeding tube probably displeased the taste experience, which may decline the QOL slightly.

It was found that problems with shoulder received significant difference. By inspecting the scores date against patients' records, we found out that the four patients with the worst shoulder scores had terrible general condition. As for those patients with decreased scores, two of them underwent accessory nerve snipped. We hypothesized the performance of neck dissection as one possible reason, which might bring about the excision or destruction of accessory nerve. The other reason might be the preparation of latissimus dorsi flaps or pectoralis major myocutaneous flaps because the truncated tissue contributed to the dysfunction.

Dry mouth is a significant manifestation of salivary gland dysfunction, confirmed as the side effect after radiotherapy[25] and reduced salivary production or sticky saliva was associated with the decline in QOL. [26] In our study, significant differences of sticky saliva and dry mouth can be found between preoperative-scores and postoperative-scores with a tendency to become more severe. Surprisingly, we found patients received radiotherapy accompanied with worse function of salivary gland and their postoperative scores of domain "sticky saliva" differed significantly to those in patients have not received radiotherapy ( $p \leq 0.001$ ). We speculated that radiotherapy might be a possible cause, combined with excision of parotid gland and submandibular gland.

Several previous studies indicated the high rates of complications after SS in head and neck cancer ranged from 23–67% and pharyngo-cutaneous fistula was the most common one.[14, 27] Complications after SS in our study, however, were seldom with only 3 patients, manifested in maxillofacial edema, flap crisis, bone exposure and pharyngo-cutaneous fistula. We considered the inconsistent result was relevant to small sample size and recall bias with some postoperative follow-up information were provided by family members of patient and sorrow of relative's loss might influence the reminiscence.

We tentatively estimated survival time and found that patients underwent salvage surgery achieved 2-year overall and disease-free survival of 52% and 24% respectively and sharply reduced 5-year overall and disease-free survival of 5% in both. The latter is lower than previous study outcomes.

Limitations do exist in this study. Limited sample size is worrying due to the rarity of patients. Because of the terrible physical condition of some patients that cannot come back to the hospital, some postoperative follow-up date were obtained through telephone, which undoubtedly increased the inaccuracy of the date. Likewise, criterion for responses to the question differs from each patient due to the subjective character. Conservative Chinese caused missing value of sexuality as well.

## Conclusions

The quality of life after salvage surgery for extensively recurrent head and neck cancer is acceptable. Despite the dysfunctions such as dysphagia and dry mouth, it does relieve the pain and improve the

short-term overall QOL of patients. Further studies on quality of life before and after salvage surgery in HNSCC are obviously needed. In the future, postoperative functional recovery training also needs attention during follow up.

## Declarations

The patient provided written informed consent.

## Conflict of interest

The authors declare that they have no conflicts of interest to this work.

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## Figures

### Figure 1

Flow chart of identification of eligible patients.

### Figure 2

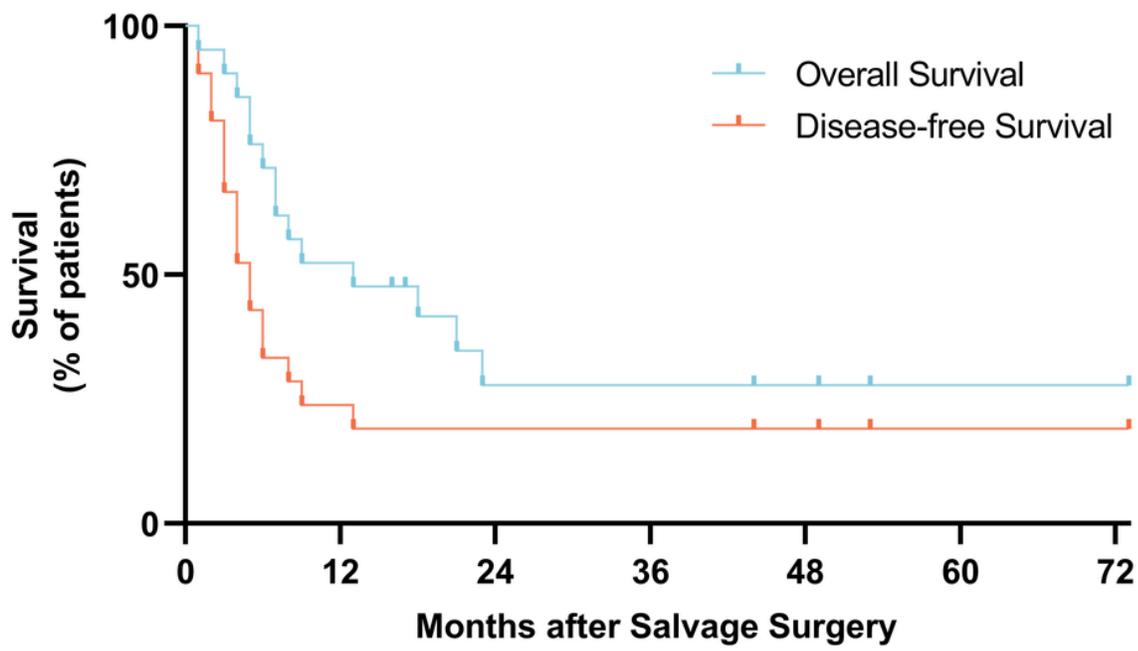
A typical salvage surgery case. A-C. primary tumor outside and inside the mouth; D-E. radiographic images presented tumor encroached maxillary and mandibular bone, maxillary sinus and orbital floor; F. excision of tumor led to orbit exposure; G-H. reconstruction with double-skin paddle free latissimus dorsi flaps and Titanium mesh implantation of right orbit; I-J. immediate postoperative images.

### Figure 3

Mean change from preoperative scores in UW-QOL and I bars indicate 95% confidence intervals. Asterisks represent significant difference between pre- and post- scores using Wilcoxon Signed Rank Test. Significance was established as  $p \leq 0.05$ .

### Figure 4

Mean change from preoperative scores in H&N35 and I bars indicate 95% confidence intervals. Two domains (sexuality and coughing) were omitted because of no change between pre- and post- scores. Asterisks represent significant difference between pre- and post- scores using Wilcoxon Signed Rank Test. Significance was established as  $p \leq 0.05$ .



**No. at Risk**

	0	12	24	36	48	60	72
Overall survival	12	5	4	2	1		
Disease-free survival	12	2	2	1	1	1	1

**Figure 5**

Kaplan-Meier estimate of overall survival and disease-free survival of patients after salvage surgery