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RESEARCH ARTICLE



Mandibular resection in patients with head and neck cancer: acute and long-term complications after reconstruction

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ABSTRACT

Background: The treatment of head and neck cancer is an intensive multimodal treatment that has a great impact on the individual patient.

Aims/Objectives: This study aimed to evaluate acute and long-term complications associated with mandibular resections and reconstructions.

Material and Methods: We retrospectively retrieved data on complications and recurrences among patients that underwent mandibular resections and reconstructions for treating oral cavity cancer ($n = 190$ patients) and osteoradionecrosis (ORN, $n = 72$). Reconstructions included composite grafts ($n = 177$), soft tissue flaps ($n = 61$), or primary closure without any graft ($n = 24$).

Results: Forty-two patients that underwent reconstructions with composite grafts displayed serious complications (Clavien–Dindo \geq IIIa). The complication rates were similar between patients treated for oral cavity cancer and patients treated for ORN. Patients that underwent a primary closure without any graft, had a significantly lower risk of complications compared to patients that underwent the other treatments. After hospitalization, 181 patients (69%) had at least one complication.

Conclusions: A majority of patients undergoing resection and reconstruction due to oral cancer/ORN suffered from postoperative complications regardless of indication, comorbidity status or reconstruction technique. The risk of Clavien–Dindo grade IIIa–V events was significantly lower for patients treated with primary closure without grafts

Significance: The results from this study clarifies the importance of in-depth analyse prior to decision of treatment for patients with head and neck cancer.

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Head and neck cancer; mandible; resection; reconstruction; affecting factors; complications

Introduction

Head and neck cancer comprises a heterogeneous group of malignant tumours with differences in natural history, treatment, and prognosis. Although the incidence of HPV-associated oropharyngeal carcinoma has become nearly epidemic [1], oral cavity cancer remains the most frequent head and neck cancer worldwide [2]. The most common tumour within the oral cavity that affects the mandible is squamous cell carcinoma; this tumour originates from the epithelial cells that cover the tongue, the floor of the mouth, and the gingiva [3]. A malignant tumour that originates from mandibular bone tissue is considered an orphan disease, which mainly includes sarcomas [4,5].

Malignant lesions from several sites in the oral cavity can invade the mandibular bone. Advanced stage oral cancer is often treated with surgery combined with radiotherapy, and sometimes chemotherapy and/or targeted therapy is included. Surgery aims to eradicate the tumour radically, and combined treatments have been shown to increase survival.

Mandibular reconstruction primarily aims to rehabilitate the patient functionally and aesthetically. Several different techniques for mandible reconstruction have been introduced over the past few decades, and their uses have been debated. The current gold standard for functional reconstruction is a microvascular technique with autogenous bone transplants [6]. For patients with a high risk of early

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mortality, mandibular resections followed by less advanced reconstructions can be lifesaving.

Treatments that include radiotherapy run the risk of late radiotherapy consequences, including hypovascularity and hypoxia, which affect cellular activity, and collagen formation in the bone and surrounding tissues. One of the most debilitating complications of radiation therapy in patients treated for head and neck cancer is osteoradionecrosis (ORN) [7].

The present study aimed to evaluate acute and long-term complications after mandibular resections and reconstructions in patients treated for oral cavity cancer or ORN.

Materials and methods

Patient data

We reviewed medical records from four tertiary hospitals in Sweden to identify patients that underwent segmental resections of the mandible due to malignant tumour or ORN, between 2000 and 2014. We identified 262 patients (153 men and 109 women, mean age: 67 years). The four hospitals covered the middle and northern parts of Sweden and comprised a population exceeding five million. We collected the following patient data: age, sex, type of surgery, chemotherapy, donor sites for composite grafting, and duration of the surgical procedure (Table 1). All data were recorded in a web-based database designed by the authors.

We identified three reconstruction techniques: primary closure without any graft, soft-tissue flap, and composite

flap. The surgical technique was based on tumour status, comorbidity, and performance status. Treatment plans were determined by a multidisciplinary tumour board, according to national and international praxis. We recorded data on comorbidities, tumour stage, and tumour site (i.e. gingiva, mandibular bone, floor of the mouth, tongue, or bucca).

Complications of the mandibular reconstruction were classified as early or late. Early complications occurred during the hospitalization period at the tertiary referral hospital and were graded according to Clavien–Dindo classifications [8]. Late complications occurred after the initial hospitalization period and at least one month post-surgery, and comprised ORN, pathological mandibular fractures, transcutaneous oral fistula, pain, patient-reported trismus, osteosynthesis fracture, osteosynthesis material-related infection, and exposed osteosynthesis material. Age as a risk factor was in the present cohort assessed with a cut-off value of 65 years between young and old.

The study was performed according to the ethical standards of the Declaration of Helsinki, and it was approved by the Regional Ethical Review board in Umeå (Dnr: 2012-250-31 M, 2013-232-32 M, 2014-197-32 M).

Statistical analysis

Patients were divided into groups based on reconstruction techniques and indications. Complication rates were compared between groups. Categorical variables were compared with Fisher's exact test. Continuous variables were compared with linear regression models (ANOVA). Associations between the early (Clavien–Dindo grade) and late complications and the various risk factors were assessed with unconditional logistic regression models. Results from these models are expressed as odds ratios and 95% confidence intervals (95% CI). *P*-values from these models were calculated with Wald tests.

Survival times were calculated from the date of mandibular resection to the date of death or December 31, 2016, whichever came first. Recurrence-free survival was calculated from the date of operation to the earliest date of recurrence, death, or December 31, 2016.

Survival was estimated with the Kaplan–Meier technique and expressed as the cumulative incidence. The time to death or failure was compared between groups with the log-rank test. Associations between clinical factors and time to death were modelled with proportional hazards regression, and results are expressed as the hazard ratio and 95% CI. All multivariate models included all of the factors listed in the corresponding tables. In all statistical analyses, *p*-values <.05 were considered significant.

Results

Sample

Of 262 patients that required segmental mandibular resections, 190 (72%) had oral cavity cancer and 72 (28%) had ORN (Table 2). Primary closures without grafts required significantly

Table 1. Characteristics of the 262 patients included in the study.

Variable	Patients ^a
Sex	
Male	153 (58%)
Female	109 (42%)
Age, years [SD]	67 (12)
Body mass index, kg/m² [SD]	25 (21)
Indication for surgery	
Osteoradionecrosis (ORN)	72 (28%)
Primary tumour	190 (72%)
Comorbidity	
No	71 (27%)
≥1	191 (73%)
Tumour site	
Gingiva	131 (50%)
Primary bone	25 (9.6%)
Floor of the mouth	38 (14.6%)
Tongue	26 (10%)
Bucca	15 (5.7%)
Other (oropharynx, salivary gland)	26 (10.0%)
Missing data	1
Tumour stage	
0	1* (0.4%)
I	18 (7.5%)
II	32 (13.3%)
III	25 (10.4%)
IVA	161 (67.1%)
IVB	2 (0.8%)
IVC	1 (0.4%)
Missing	22
Smoking at the time of surgery	
Never smoked	90 (36.9%)
Former smoker	109 (44.7%)
Smokers	45 (18.4%)
Missing data	18

^aData are given as n (%) or the mean (SD); *ORN.

Table 2. Patient and surgical characteristics for three reconstruction techniques.

Variable	Primary closure without graft	Soft tissue reconstruction	Composite graft reconstruction	P-value
Age, years	72.8 (13)	73.1 (10.4)	63.7 (12)	<.001
Sex				.48
Male	13 (54.2%)	32 (52.5%)	108 (61%)	
Female	11 (45.8%)	29 (47.5%)	69 (39%)	
Tumour site				.57
Gingiva, primary bone	12 (50%)	36 (59%)	108 (61.4%)	
Floor of the mouth, tongue, bucca	12 (50%)	25 (41%)	68 (38.6%)	
Tumour stage				.017
0, I, II	5 (21.7%)	5 (8.6%)	41 (25.8%)	
III, IV	18 (78.3%)	53 (91.4%)	118 (74.2%)	
Operation time, hours	4.4 (2.7)	9.4 (2.9)	11.5 (2.9)	<.001
Comorbidity				<.001
None	4 (16.7%)	6 (9.8%)	61 (34.5%)	
≥1	20 (83.3%)	55 (90.2%)	116 (65.5%)	
Total number of patients	24	61	177	

Data are given as *n* (%) or the mean (SD).

Table 3. Descriptions of composite grafts in 177 patients and soft tissue flaps in 61 patients.

Composite grafts	Number
Fibula	164
Radius	8
Iliac crest	3
Scapula	2
Soft tissue grafts	
Pectoralis major	33
Radial forearm flap	16
Anterolateral thigh	6
Missing	6

shorter operation times than the other reconstruction techniques. Patients that received composite grafts were younger and had less comorbidities than patients in the other groups. Table 3 describes the different vascularized composite bone grafts and soft tissue flaps used in composite graft treatments.

Three patients experienced events that led to death during the postoperative hospital stay. Sixty-three patients (24%) had Clavien–Dindo grade IIIa or higher complications, and 181 (69%) patients had one or more late complications. The risk of Clavien–Dindo grade IIIa–V events was significantly lower for patients treated with primary closure without any grafts, compared to patients treated with soft-tissue reconstructions ($p = .049$) or composite grafts ($p = .028$). The Clavien–Dindo grades of surgical complications were similar between patients treated for oral cavity cancer ($n = 119$) and those treated for ORN ($n = 48$).

We performed multivariate unconditional logistic regression model analyses to evaluate whether early complications, late complications, and cancer recurrences were associated with age, sex, tumour site, tumour stage, reconstruction technique, and comorbidity (Table 4). For patients under 65 year the risk for late complications was significantly higher ($p = 0.022$). Patients with tumour stage 0–II demonstrated a significantly higher risk of late complications ($p = .034$). The incidence of cancer recurrence was significantly higher in patients aged <65 years ($p = .022$), women ($p = .028$), patients with tumours originating from the gingiva and primary bone versus other sites ($p = .039$), and patients treated for primary tumours versus ORN ($p < .001$). Among the 190 patients that underwent resections of a primary tumour, 136 received additional radiotherapy. The complications and recurrence rates

Table 4. Multivariate analysis of the risk of complications and recurrence.

	Clavien–Dindo OR 95% CI Wald <i>p</i> value	Late complications OR 95% CI Wald <i>p</i> value	Recurrence of cancer OR 95% CI Wald <i>p</i> value
Main effects			
>65 years old	1.40 [0.73, 2.67]	0.49 [0.27, 0.90]	0.47 [0.24, 0.90]
Females	.316 [0.67, 2.41]	.022 [0.56, 1.86]	.028 [1.08, 3.72]
Site in mouth ^a	.470 [0.82, 3.14]	.947 [0.54, 1.88]	.028 [0.25, 0.97]
Stage III–IV ^b	1.61 [0.70, 3.52]	.039 [0.19, 0.94]	.039 [0.45, 1.98]
Soft tissue ^c	.163 [1.01, 66.52]	.985 [0.33, 2.80]	.034 [0.27, 2.27]
Composite grafts ^d	.275 [1.28, 78.80]	.034 [0.32, 2.29]	.869 [0.18, 1.32]
Comb1+ ^e	.049 [0.64, 2.72]	.949 [0.50, 1.89]	.656 [0.27, 1.05]
dF	7	7	7
Chi2	9.7	11.5	16.7
<i>P</i>	.209	.117	.019
<i>N</i>	239	239	239

Early complications (Clavien–Dindo grades ≥ IIIa), late complications, and cancer recurrence were analysed in relation to the following factors: age, sex, tumour site, tumour stage, reconstruction technique, and comorbidity. All listed factors were included in the multivariate analysis. Significant outcomes highlighted with bold letter type. OR: odds ratio.

^aSite: tongue, floor of the mouth, and bucca sites versus gingiva and primary bone sites.

^bTumour stages III–IV versus tumour stages 0–II.

^cSoft tissue flap versus primary closure.

^dComposite grafts versus primary closure.

^eOne or more comorbidities versus no comorbidity.

were similar for patients that received preoperative ($n = 46$) and postoperative ($n = 90$) radiotherapy.

The median follow-up for all 262 patients was 7.8 years (1.4–17 years). During the follow-up period, 170 patients died. The median times to all-cause death were 3.0 years, for the oral cavity cancer group, and 6.5 years for the ORN group. A multivariate Cox regression analysis of overall survival showed that stage III–IV tumours significantly increased the risk of death ($p = .034$). The cumulative

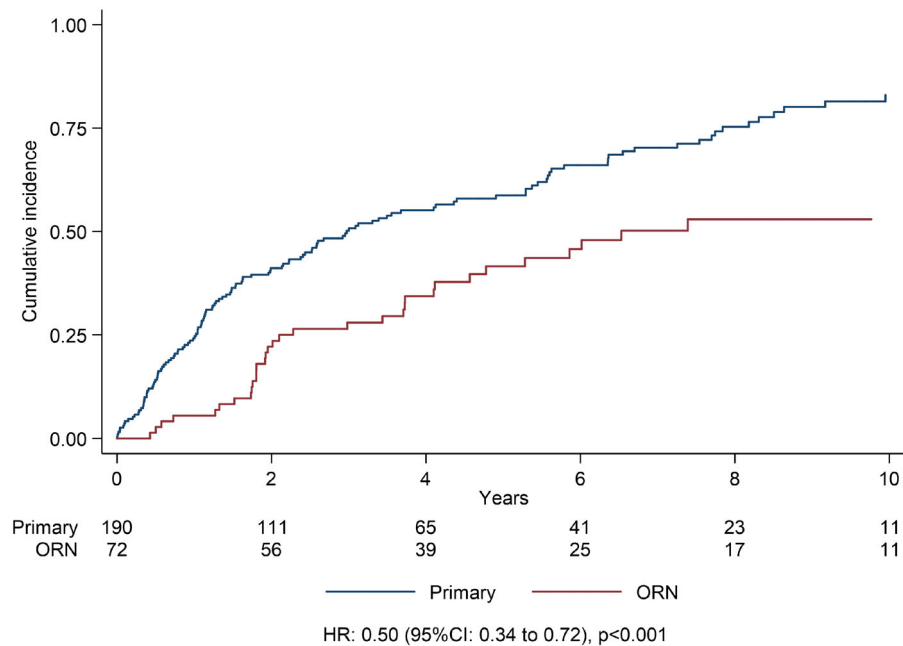


Figure 1. Cumulative incidence of death after mandibular reconstruction treatments for a primary tumour ($n=190$ patients) or osteoradionecrosis (ORN; $n=72$ patients).

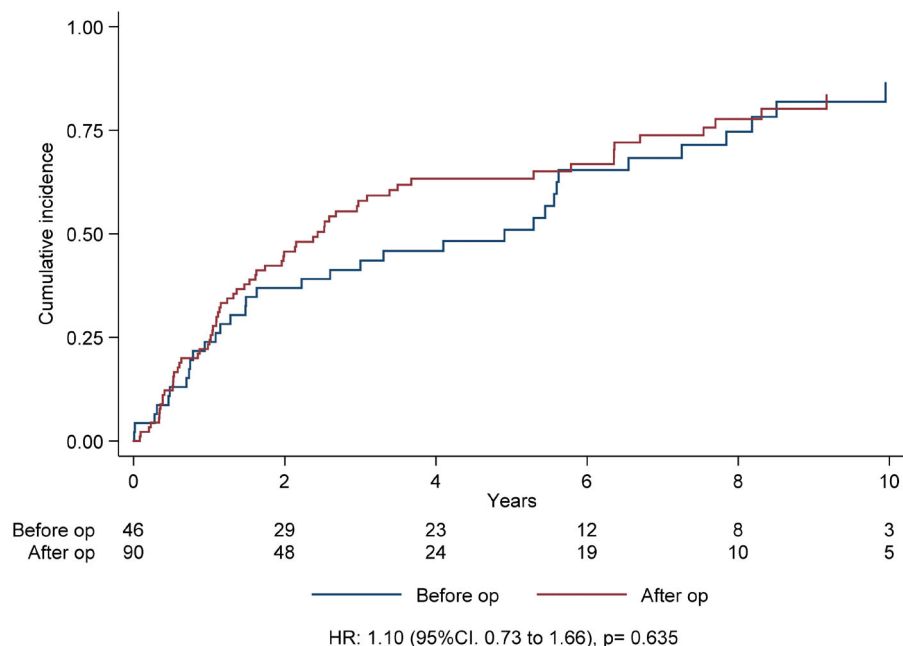


Figure 2. Cumulative incidence of death in 46 patients treated with preoperative radiotherapy and 90 patients treated with postoperative radiotherapy.

incidence of death was significantly higher in the primary cancer group than in the ORN group (Figure 1). Among patients with oral cavity cancer, the cumulative incidence of death was not significantly different between patients that received preoperative ($n=46$) and those that received postoperative ($n=90$) radiotherapy (Figure 2).

Discussion

This retrospective study evaluated acute and long-term complications after mandibular resections and reconstructions in

patients with oral cavity cancer (72%) or ORN (28%). Most reconstructions (67%) were performed with a composite graft, primarily a free vascularized fibula graft. Nearly one quarter of patients (23%) received soft tissue reconstruction. Few patients (9%) received primary closure without grafts, which resulted in a relatively shorter surgery. These patients tended to be older and had a lower rate of serious postoperative complications, compared to the two other groups. These findings indicated that the more vulnerable patients benefited from less advanced reconstructions, as reflected by the low complication rate.

We used the Clavien–Dindo classification to define early complications [9]. We found that the serious complication (Clavien–Dindo \geq IIIa) rates were similar between patients treated for oral cavity cancer and those treated for ORN. This finding was consistent with two previous studies [10,11] that reported approximately the same complication rates after free-flap reconstructions in patients with oral cancer and patients with oropharyngeal cancer. In the present study, we observed total or partial flap failure in 14% of patients.

A current issue of concern is how to treat oral cancers that involve the mandible in patients with a high risk of perioperative death. We showed that the incidence of Clavien–Dindo grade IIIa–V was lower in patients with primary closure than in patients that received other techniques. In addition, we found no association between age or comorbidity and the incidence of early complications. Similarly, Blackwell et al. [12] showed that the incidence of medical and reconstructive complications did not differ between older and younger patients. However, our finding that primary closure was associated with a lower incidence of general complications may be most relevant to older, more vulnerable patients that might not tolerate a free-flap operation.

The literature offers little information about the success rates and long-term complications associated with mandibular reconstructions. Indeed, the use of reconstruction plates without bony reconstruction runs high risks of postoperative oral incompetence and hardware exposure [5,13]. Postoperative oral incompetence commonly reduces the physical function and results in oral disability. One shortcoming of this retrospective study is that we had no viable data on oral function. This topic must be analysed in a prospective study on patients undergoing mandibular resection and reconstruction.

In our cohort, over two-thirds of patients experienced at least one late complication. Moreover, we found that patients <65 years old and patients with an initially low tumour stage were at increased risk of late complications. We also found that the risk of cancer recurrence was significantly increased in patients <65 years of age, women, patients with tumours that originated from the gingiva and primary bone, and patients treated for oral cavity cancer (compared to those treated for ORN). It has been questioned whether, in the surgical management of head and neck cancer, mandibular microvascular reconstruction can be justified for older patients [14]. Dimovska et al. [15] suggested that comorbidity status should be the primary guide for surgical decision-making. However, in the present study, we found that comorbidity did not affect survival; the only prognostic factor for death was the initial tumour stage.

We found that the choice between preoperative and postoperative irradiation did not significantly impact the cumulative incidence of death in patients treated for oral cavity cancer. Previously, both Tall et al. [16] and Mucke et al. [17] found that preoperative radiotherapy was associated with an increased risk of flap failure. Consequently, Tall

et al. [16] recommended postoperative radiotherapy, when possible, or early reconstruction after radiotherapy.

The results from this retrospective study indicated that mandibular reconstruction was associated with a high incidence of complications, regardless of the indication, comorbidity status, and reconstruction technique. More comprehensive research is needed on late complications in mandibular reconstruction [18].

In future, other factors, such as the oral cavity site, the effect on oral function, patient age, and the volume of bony free flaps, should be studied in a prospective manner to identify which patients are most likely to benefit from a given surgical treatment.

Methodological considerations/limitations

This study had some limitations. First, due to the retrospective approach, we might have underestimated the number of eligible patients, due to inconsistencies in reporting at the four tertiary hospitals. Second, our patients were treated over a period of 15 years. Thus, different surgeons could have been involved in patient care.

Disclosure statement

The authors declare no financial or personal relationships with other people or organizations that could inappropriately influence this study. Conflicts of interest: none. All authors have approved the final article.

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