Received: 20 January 2020 | Accepted: 22 May 2020

DOI: 10.1002/jso.26054

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Locoregional recurrence rate and disease-specific survival following marginal vs segmental resection for oral squamous cell carcinoma with mandibular bone invasion

Celine C. Stoop DMD[1] | Remco de Bree MD, PhD[2] | Antoine J.W.P. Rosenberg DMD, MD, PhD[1] | Jan T.M. van Gemert DMD, MD, PhD[2] | Tim Forouzanfar DMD, MD, PhD[3] | Ellen M. Van Cann DMD, MD, PhD[1,2,3]

[1]Department of Oral and Maxillofacial Surgery and Special Dental Care, University Medical Center Utrecht, the Netherlands

[2]Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht, the Netherlands

[3]Department of Oral and Maxillofacial Surgery/Oral Pathology, VU University Medical Center/Academic Center for Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands

Correspondence
E.M. Van Cann, Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.
Email: e.m.vancann@umcutrecht.nl

Abstract

Background and Objectives: To determine locoregional recurrence rate (LRR) and disease-specific survival (DSS) following marginal vs segmental mandibulectomy.

Methods: Included were 210 patients, who had marginal or segmental mandibulectomy between 2000 and 2017. Marginal resection was performed when complete removal of the tumor was deemed feasible on the condition that at least 1 cm bone height of the inferior border of the mandible could be preserved. Segmental resection was performed in case less than 1 cm bone height of the mandible would remain. Clinical and histopathological data were collected from medical records. LRR and DSS were computed using Kaplan-Meier analysis. Cox-regression analysis was used to identify risk factors for LRR and DSS.

Results: A total of 59 marginal and 151 segmental resections had been performed. There was no significant difference in 3- and 5-year LRR ($P = .904$) and no significant difference in 3- and 5-year DSS ($P = .362$) between the marginal and segmental resection group. Cox-regression analysis showed a trend for surgical margin less than equal to 1 mm, to affect LRR ($P = .05$) and surgical margin less than equal 1 mm, perineural invasion and lymph node metastasis to affect DSS ($P < .05$).

Conclusions: There was no difference in outcome between the two types of mandibulectomy.

KEYWORDS

bone invasion, fracture, mandibulectomy, oral cancer, osteoradionecrosis, protocol

1 | INTRODUCTION

Each year approximately 300 000 new cases of oral cancer are diagnosed worldwide.[1] Oral squamous cell carcinoma (OSCC) is the most common malignant tumor of the oral cavity.[1] OSCC can invade the mandible when located in close proximity to the bone. Surgery is the first-choice treatment for OSCC, with the aim to completely remove the tumor. If OSCC invades the mandible, the affected bone needs to be resected in continuity with the tumor in the soft tissues. There are two types of mandibular resection: segmental resection and marginal resection. Segmental resection is a resection involving the entire vertical height of the mandible with interruption of the continuity of the mandible. Marginal

resection is a resection involving part of the height of the mandible with preservation of the continuity of the mandible. The indication for segmental resection and marginal resection is often debated, as well as the extent of the resection.[2-6] There is no guideline based on evidence, that could assist in the decision about the type of mandibular resection. A future guideline should be oncologically safe on the one hand to minimize the risk of irradical resection and avoid unnecessary removal of bone, on the other hand, to preserve function, aesthetics, and quality of life.[2] To develop such a guideline, outcomes are necessary, like locoregional recurrence rate (LRR) and disease-specific survival (DSS) following marginal and segmental resection for OSCC.

The aim of this study is to determine LRR and DSS in patients who underwent marginal and segmental resection for OSCC with the histopathologically confirmed invasion of mandibular bone. Our hypothesis is that there is no difference in LRR and DSS between patients who underwent marginal and segmental resection for OSCC with the histopathologically confirmed invasion of mandibular bone.

2 | MATERIALS AND METHODS

2.1 | Study design, inclusion, and exclusion criteria

A retrospective cohort study was conducted. This study was exempted from an ethical review of the University Medical Center Utrecht (Reg.No: 19-401/C).

Included were patients who had undergone marginal or segmental resection at a single center with a head and neck cancer service, the University Medical Center Utrecht, between January 2000 and December 2017 for first primary OSCC, with mandibular invasion confirmed by histopathological examination of the resection specimen.

Excluded were patients lost to follow up within 12 months, and patients with missing clinical or histopathological information other than invasive growth pattern or tumor grade.

2.2 | Preoperative assessment

For preoperative screening, we performed orthopantomogram (OPT), computed tomography or magnetic resonance imaging, and bone single photon emission computed tomography (SPECT) on the indication. The extensive bone invasion was made visible on the OPT, whereas computed tomography or magnetic resonance imaging could reveal more subtle bone invasion. On indication bone, SPECT was used to rule out mandibular invasion, as bone SPECT has 100% sensitivity, as described in a previous publication.[4]

2.3 | Treatment protocol for the type of mandibular resection

Marginal resection was performed when complete removal of the tumor in the bone and soft tissues was deemed feasible, on the condition that at least 1 cm bone height of the inferior border of the mandible could be preserved. Segmental resection was performed in case less than 1 cm bone height of the inferior border of the mandible was estimated to remain.

2.4 | Data collection

The following data were collected from medical records: sex, age, tumor location, tumor size (largest diameter measured in any direction), infiltration depth, tumor grade, invasive growth pattern, vascular or lymphovascular invasion, perineural invasion, lymph node metastasis, type of mandibular resection, surgical margin (≤1 and >1 mm), adjuvant therapy, date of locoregional recurrence, date of distant metastasis, date, and cause of death. Brown's classification for segmental mandibular defects was used to classify the segmental resections and the location of the corresponding tumors. Because no system exists to classify marginal mandibular defects, we used Brown's classification also for marginal resections to classify the horizontal position of the corresponding tumors. In case osteoradionecrosis (ORN) or fracture occurred after marginal resection, additional data were collected: sex, age, date of diagnosis, area of ORN or fracture, cause of ORN or fracture, the height of the remaining mandible, and preservation of the inferior alveolar nerve.

2.5 | Statistical analyses

Statistical analyses were run using SPSS software for Windows (IBM SPSS Statistics, Version 25.0. Armonk, NY). The distribution of several variables was compared using the χ^2 test or independent t test. DSS was defined as the time from diagnosis until death or date last seen alive and was estimated by Kaplan-Meier analysis. To compare survival curves, the log rank (Mantel-Cox) test was used. Cox regression analysis was used to identify factors associated with LRR and DSS. Statistical significance was set at $P < .05$.

3 | RESULTS

Between January 2000 and December 2017, 229 patients had undergone mandibular resection for OSCC with mandibular bone invasion confirmed by histopathological examination of the resection specimen. Nineteen of the 229 patients with mandibular invasion were lost to follow-up within 12 months. The remaining 210 patients were included in the study. From these 210 patients, 59 patients had a marginal resection and 151 had a segmental resection.

Table 1 shows the baseline characteristics of the study population.

Sex, age, tumor grade, invasive growth pattern, vascular or lymphovascular invasion, perineural invasion, lymph node metastasis, surgical margin, adjuvant therapy, and cause of death were evenly distributed between the marginal and segmental resection group. Tumor location, tumor size and infiltration depth (mm) were

TABLE 1 Clinical data (patient and tumor variables), distribution over marginal and segmental resection group

	Number	Marginal resection	Segmental resection	*P* value
Sex				.095
Male	127	41 (32.28%)	86 (67.72%)	
Female	83	18 (21.69%)	65 (78.31%)	
Age				.460*
Mean (SD)		66.53 (10.73)	65.17 (12.37)	
Tumor location (Brown's classification)				***.000***
I	66	32 (48.48%)	34 (51.51%	
Ic	3	0 (0.00%)	3 (100%)	
II	58	3 (5.17%)	55 (94.83%)	
III	58	23 (39.66%)	35 (60.34%)	
IV	25	1 (4.00%)	24 (96.00%)	
Tumor size, mm				***.001*** *
Mean (SD)		30.09 (13.50)	38.50 (16.50)	
Infiltration depth (mm)				***.000*** *
Mean (SD)		12.18 (7.01)	21.21 (13.17)	
Tumor grade				.242
Well	27	6 (22.22%)	21 (77.78%)	
Moderate	128	37 (28.91%)	91 (71.09%)	
Poor	17	2 (11.76%)	15 (88.24%)	
Unknown	38	14 (36.84%)	24 (63.16%)	
Invasive growth pattern				.371
Cohesive	32	8 (25.00%)	24 (75.00%)	
Unfavorable	114	31 (27.19%)	83 (72.81%)	
Remaining	5	0 (0.00%)	5 (100%)	
Unknown	59	20 (33.90%)	39 (66.10%)	
Vascular/lymphovascular invasion				.666
Yes	32	10 (31.25%)	22 (68.75%)	
No	178	49 (27.53%)	129 (72.47%)	
Perineural invasion				.715
Yes	99	29 (29.29%)	70 (70.70%)	
No	111	30 (27.03%)	81 (72.97%)	
Lymph node metastasis				.721
Yes	118	32 (27.12%)	86 (72.88%)	
No	92	27 (29.35%)	65 (70.65%)	
Surgical margin				.118
>1 mm	128	31 (24.22%)	97 (75.78%)	
≤1 mm	82	28 (34.15%)	54 (65.85%)	
Adjuvant therapy				.187
Radiotherapy	136	42 (30.88%)	94 (69.12%)	
Chemoradiation	23	4 (17.39%)	19 (82.61%)	
No adjuvant therapy	51			
Deceased				.721
Yes	118	32 (27.12%)	86 (72.88%)	
No	92	27 (29.35%)	65 (70.65%)	
Cause of death				.515
Tumor-related	76	19 (25.00%)	57 (75.00%)	

TABLE 1 (Continued)

	Number	Marginal resection	Segmental resection	*P* value
Other	23	9 (39.13%)	14 (60.87%)	
Unknown	19	4 (21.05%)	15 (78.95%)	

Note: $P < .05$ is significant (*bold*). The χ^2 test performed;
*Expect independent *t* test.

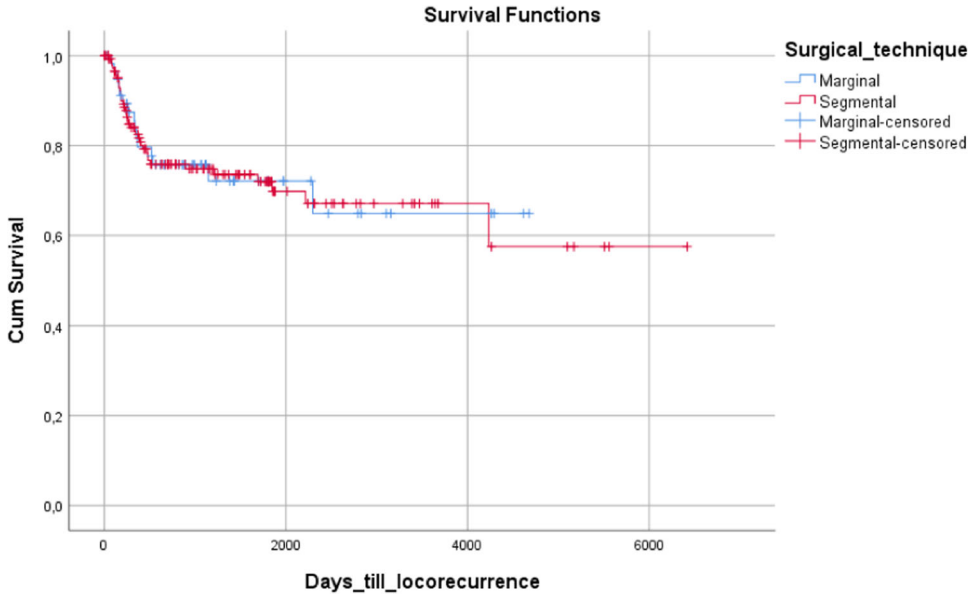

FIGURE 1 Locoregional recurrence (Kaplan-Meier) [Color figure can be viewed at wileyonlinelibrary.com]

unevenly distributed between the marginal and segmental resection group: the segmental resection group contained more mandibular defects classified as Brown's class Ic, II, and IV ($P = .000$), larger tumors ($P = .001$) and tumors with increased infiltration depth ($P = .000$) than the marginal resection group. In this study population, there were no mandibular defects classified as Brown's class IIc and IVc.

3.1 | Locoregional recurrence rate

Three-year LRR was 20.3% in the marginal resection group and 21.9% in the segmental resection group ($P = .716$) (Figure 1 and Table 2). The 5-year LRR was 22.0% in the marginal resection group and 23.2% in the segmental resection group ($P = .783$) (Figure 1 and Table 2). The log

TABLE 2 Kaplan-Meier estimated locoregional recurrence rate and disease-specific survival

LRR	Three-y LRR this study vs literature	Five-y LRR this study vs literature
Marginal resection	20.3% vs 25.0-29.1%[7,8]	22.0% vs 17-39.7%[7,9]
Segmental resection	21.9% vs 18.4%[7]	23.2% vs 14-34.2%[7,9]
P value	.716/n.a.	.783/n.a.
DSS	**Three-y DSS this study vs literature**	**Five-y DSS this study vs literature**
Marginal resection	72.9% vs 75.2%[7]	69.5% vs 55.5%[7]
Segmental resection	66.2% vs 69.2%[7]	64.2% vs 60.7%[7]
P value	.287/n.a.	.391/n.a.

Abbreviations: DSS, disease-specific survival; LRR, locoregional recurrence rate; NA, not applicable.

TABLE 3 Cox regression to analyze potentially predictive factors for locoregional recurrence rate

Potentially predictive factors	Hazard ratio (95% CI)	*P* value
Sex	0.677 (0.358-1.280)	.230
Age	0.996 (0.967-1.025)	.771
Tumor size	1.013 (0.995-1.032)	.154
Infiltration depth	1.004 (0.978-1.032)	.749
Lymph node metastasis	0.886 (0.462-1.697)	.714
Tumor grade		.313
Vascular/lymphovascular invasion	0.716 (0.316-1.620)	.422
Perineural invasion	0.888 (0.449-1.754)	.732
Type of mandibular resection	0.931 (0.447-1.937)	.848
Surgical margin ≤1 mm	1.888 (0.999-3.570)	***.050***
Adjuvant therapy	1.003 (0.426-2.362)	.994

Note: *P* = .05 is a trend (bold).

rank test showed no significant difference in LRR between the marginal and segmental resection group (*P* = .904).

Cox regression analysis showed a trend for a surgical margin less than equal to 1 mm to affect LRR (*P* = .05) (Table 3).

3.2 | Disease-specific survival

Three-year DSS was 72.9% in the marginal resection group and 66.2% in the segmental resection group (*P* = .287) (Figure 2 and Table 2). Five-year DSS was 69.5% in the marginal resection group and 64.2% in the segmental resection group (*P* = .391) (Figure 2 and Table 2). The log-rank test showed no significant difference in DSS between the marginal and segmental resection group (*P* = .362). Cox regression analysis showed that DSS was affected by a surgical margin less than equal to 1 mm (*P* = .003), perineural invasion (*P* = .013), and lymph node metastasis (*P* = .015) (Table 4).

3.3 | Osteoradionecrosis and fracture after marginal resection

In 5 out of 59 patients who had a marginal resection, ORN, and/or fracture occurred. The pertinent data are shown in Table 5. Two patients had ORN, one patient had a mandibular fracture and two patients had ORN with pathological fracture. In four cases, the marginal resection had been made with the right angle. The remaining height of mandible after marginal resection ranged between 10 and 17 mm and the inferior alveolar nerve had been killed in one case.

4 | DISCUSSION

Our hypothesis is confirmed in our study group that there was no difference in 3- and 5-year LRR and 3- and 5-year DSS between patients who underwent marginal resection or segmental resection for OSCC with histopathologically confirmed mandibular invasion; marginal resection was performed on the condition that 1 cm of bone height was preserved.

4.1 | Locoregional recurrence rate

LRR in our study group was comparable with figures reported in the literature[7,10,11] (Table 2). We found no difference in LRR between the marginal and segmental resection group in patients with bone invasion of the mandible. This finding is in accordance with previous

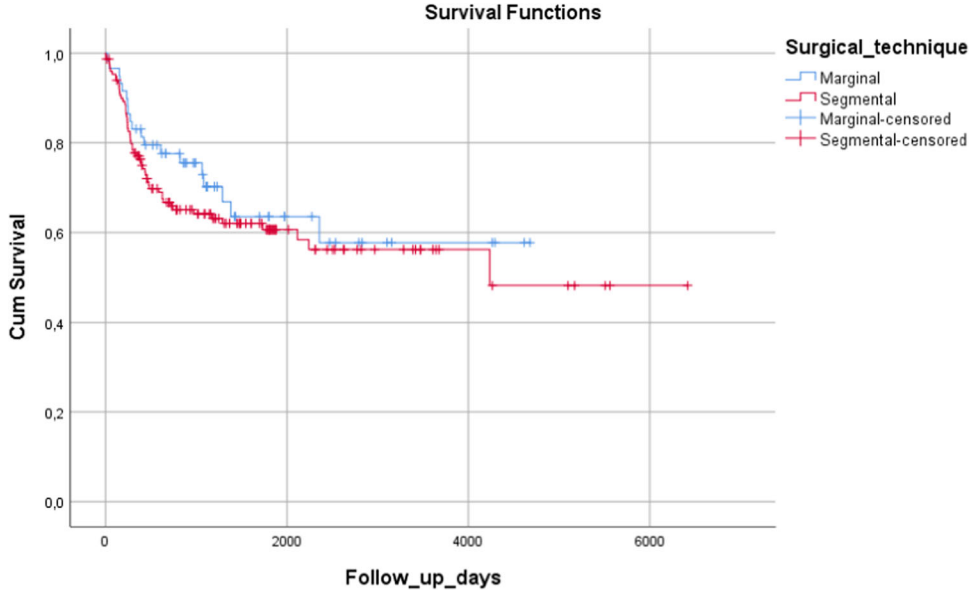

FIGURE 2 Disease-specific survival (Kaplan-Meier) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Cox regression to analyze potentially predictive factors for disease-specific survival

Potentially predictive factors	Hazard ratio (95% CI)	*P* value
Sex	0.954 (0.510-1.784)	.884
Age	0.990 (0.962-1.018)	.466
Tumor location (Brown's classification)		.563
Tumor size	1.008 (0.991-1.026)	.337
Infiltration depth	1.002 (0.978-1.028)	.854
Lymph node metastasis	0.399 (0.190-0.837)	**.015**
Tumor grade		.294
Vascular/lymphovascular invasion	0.974 (0.462-2.050)	.944
Perineural invasion	0.431 (0.222-0.838)	**.013**
Type of mandibular resection	0.529 (0.236-1.185)	.122
Surgical margin ≤1 mm	2.631 (1.401-4.940)	**.003**
Adjuvant therapy	1.192 (0.518-2.741)	.680

Note: $P < .05$ is significant (bold).

studies.[7,9-11] Our study showed a trend for surgical margin less than equal to 1 mm to affect LRR ($P = .05$), whereas Guerra et al[12] found a significant association between positive margin and tumor size and LRR.

4.2 | Disease-specific survival

DSS in our study was comparable with the figures reported in the literature[7] (Table 2).

We found no difference in DSS between the marginal and segmental resection group in patients with bone invasion of the mandible. This finding is in accordance with previous studies.[8,9,11,13] Our study showed that DSS was affected by a surgical margin ($P = .003$), perineural invasion ($P = .013$), and lymph node metastasis ($P = .015$). Other studies reported that survival was associated with tumor location,[14] tumor size,[15] tumor grade,[7,14] tumor stage,[8,14] lymph node metastasis[14] and positive margins.[8,14]

4.3 | Type of resection

Current knowledge of mandibular resection is mainly based on studies with low level of evidence such as retrospective studies, nonrandomized studies or case-series.[6-8] Our study also had a retrospective design, and inherent to the retrospective design of the study was the different composition of the two groups: the segmental resection group had larger tumors and increased infiltration depth than the marginal resection group. The different composition of the groups hampers comparison of the treatment effect, which is the outcome after marginal vs segmental resection. Nonetheless, the outcomes following marginal resection for OSCC invading the mandible were not worse than following segmental resection, and increased infiltration depth did not correlate with LRR or DSS. The finding that there was no difference in outcome between the marginal and segmental resection group, might indirectly indicate that marginal resection can be oncologically safe when complete removal of the tumor is deemed feasible and at least 1 cm bone height of the inferior border of the mandible is preserved. We recommend segmental resection if less than 1 cm bone height of the mandible would remain.

In the future, a prospective study, ideally a randomized controlled trial, could be carried out to compare the outcomes of the two types of mandibular resection with a higher level of evidence.

5 | CONCLUSION

There was no difference in LRR and DSS between marginal and segmental resection for OSCC invading the mandible. Marginal resection can be safe when complete removal of the tumor is deemed feasible and at least 1 cm bone height of the inferior border of the mandible is preserved. We recommend segmental resection if less than 1 cm bone

TABLE 5 Osteoradionecrosis and fracture after marginal resection

ORN/#	Sex	Age, y	PORT	Time until ORN/#, mo	Area of ORN/#	Cause of ORN/#	Remaining bone height, mm	Preservation of inferior alveolar nerve
ORN	f	49	Yes	25	Anterior	Dental implant	17	Yes
ORN	f	66	Yes	7	Body	Right angle[a]	13	Yes
#	m	63	Yes	26	Body	Right angle[b]	10	No
ORN +#	m	63	Yes	28	Body	Right angle[a]	10	Yes
ORN +#	m	66	Yes	23	Body	Right angle[b]	14	Yes

Note: #, fracture; Anterior, anterior mandible; Body, mandibular body.
Abbreviations: ORN, osteoradionecrosis; PORT: postoperative radiotherapy.
[a]Means marginal resection performed with the right angle, combined with a mandibular split osteotomy.
[b]Means marginal resection performed with the right angle.

height of the mandible would remain. Perineural invasion, lymph node metastasis, and surgical margin less than equal to 1 mm affected DSS of patients with OSCC and mandibular invasion.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

ORCID

Celine C. Stoop http://orcid.org/0000-0003-4355-8226
Ellen M. Van Cann http://orcid.org/0000-0002-1999-5074

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144:1941-1953.
2. Van Cann EM, Dom M, Koole R, Merkx MAW, Stoelinga PJW. Health related quality of life after mandibular resection for oral and oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2005;41:687-693.
3. Van Cann EM, Oyen WJ, Koole R, Stoelinga PJ. Bone SPECT reduces the number of unnecessary mandibular resections in patients with squamous cell carcinoma. *Oral Oncol*. 2006;42:409-414.
4. Van Cann EM, Koole R, Oyen WJG, et al. Assessment of mandibular invasion of squamous cell carcinoma by various modes of imaging: constructing a diagnostic algorithm. *Int J Oral Maxillofac Surg*. 2008;37:535-541.
5. Hendrikx AWF, Maal T, Dieleman F, Van Cann EM, Merkx MAW. Cone-beam CT in the assessment of mandibular invasion by oral squamous cell carcinoma: results of the preliminary study. *Int J Oral Maxillofac Surg*. 2010;39:436-439.
6. Kansy K, Mueller AA, Mücke T, et al. A worldwide comparison of the management of surgical treatment of advanced oral cancer. *J Craniomaxillofac Surg*. 2018;46:511-520.
7. Qiu Y, Lin L, Shi B, Zhu X. Does different mandibulectomy (marginal vs segmental) affect the prognosis in patients with oral squamous cell carcinoma? *J Oral Maxillofac Surg*. 2018;76:1117-1122.
8. De Vicente JC, Recio OR, Pendás SL, López-Arranz JS. Oral squamous cell carcinoma of the mandibular region: a survival study. *Head Neck*. 2001;23:536-543.
9. Massimo Politi, Fabio Costa, Massim M. Review of segmental and marginal resection of the mandible in patients with oral cancer. *Acta Otolaryngol*. 2000;120:569-579.
10. Dubner S, Heller KS. Local control of squamous cell carcinoma following marginal and segmental mandibulectomy. *Head Neck*. 1993;15:29-32.
11. Patel RS, Dirven R, Clark JR, Swinson BD, Gao K, O'Brien CJ. The prognostic impact of extent of bone invasion and extent of bone resection in oral carcinoma. *Laryngoscope*. 2008;118:780-785.
12. Guerra MF, Campo FJ, Gias LN, Perez JS. Rim versus sagittal mandibulectomy for the treatment of squamous cell carcinoma: two types of mandibular preservation. *Head Neck*. 2003;25:982-989.
13. Muñoz Guerra MF, Naval Gías L, Campo FRg, Pérez JS. Marginal and segmental mandibulectomy in patients with oral cancer: a statistical analysis of 106 cases. *J Oral Maxillofac Surg*. 2003;61:1289-1296.
14. Woolgar JA, Scott J, Vaughan ED, Brown JS, West CR, Rogers S. Survival, metastasis and recurrence of oral cancer in relation to pathological features. *Ann Roy Coll Surg*. 1995;77:325-331.
15. Shen Q, Chen Y, Gokavarapu S, Cao W, Ji T. Primary intraosseous squamous cell carcinoma of the mandible: locoregional control and survival is significantly reduced if the tumour is more than 4 cm in size. *Br J Oral Maxillofac Surg*. 2018;56:48-53.

How to cite this article: Stoop CC, de Bree R, Rosenberg AJWP, van Gemert JTM, Forouzanfar T, Van Cann EM. Locoregional recurrence rate and disease-specific survival following marginal vs segmental resection for oral squamous cell carcinoma with mandibular bone invasion. *J Surg Oncol*. 2020;122:646–652. https://doi.org/10.1002/jso.26054