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Influence of bone invasion on outcomes after marginal mandibulectomy in squamous cell carcinoma of the oral cavity

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ABSTRACT

Introduction: Marginal mandibulectomy (MM) is indicated for oral cavity squamous cell carcinomas (OCSCC) that abut or minimally erode the mandible without gross invasion. Successful implementation of MM is predicated on accurate patient selection and appropriate adjuvant treatment based on well-known host and tumor characteristics. The incidence of microscopically diagnosed bone involvement in MM specimens and its implications on outcomes have however not been reported in large contemporary series.

Purpose: To report the incidence of bone involvement and analyze its influence on oncologic outcomes in selected patients who underwent MM in treatment of OCSCC.

Method: A retrospective cohort study was performed on a consecutive series of previously untreated patients requiring MM, at a tertiary care cancer center, between 1985 and 2012 (n = 326). The median age was 64 years and 59% were male. The majority of patients (67%) had a primary tumor of the floor of the mouth or lower alveolus, 80% were clinically staged T1-2, and 31% were clinically N+. Postoperative radiation (PORT) was used in 27% and chemoradiation (POCTRT) in 8% of patients who had microscopic bone invasion. The median follow up period was 55 months and endpoints of interest were local and regional recurrence free (LRFS and RRFS) and disease specific (DSS) survival.

Results: Microscopic bone invasion was present in 15% of patients (n = 49). Among these, cortical invasion was present in 32, medullary in 13, and it was not specified in 4. Eight patients had microscopic positive bone margins. Positive bone margins were associated with medullary bone involvement ($p < 0.001$), floor of mouth and buccal mucosa primary site ($p = 0.03$), and positive soft tissue margins ($p = 0.06$). LRFS and DSS were similar in patients without versus with bone invasion (62.8% vs 79.7% and 76.2% vs 66% respectively, p = NS). LRFS were similar in patients with microscopic positive versus negative bone margins, as long as postoperative adjuvant treatment was administered.

Conclusion: Microscopic bone involvement does not adversely influence outcomes but medullary bone involvement does confer a higher risk of positive bone margins. MM and appropriate adjuvant treatment is an effective strategy for treatment of OCSCC in selected patients with primary tumors adherent to or in proximity to the mandible.

1. Introduction

Management of the mandible is an important issue in surgical treatment of locally advanced cancers of the oral cavity that are in proximity to or have invaded the mandible. To understand the process of local progression of oral cancer that leads to invasion of the mandible, McGregor et al. studied whole-organ sections of specimens from patients undergoing composite resections for advanced oral cancers (Ariyan et al., 1995). They noted that direct infiltration through intact lingual cortex of the mandible was rare. In order for the cancer to invade the medullary space of the dentate mandible, it has to creep up to the alveolar process and then invade the medullary space through the tooth sockets. A similar mode of tumor progression was observed even in the edentulous mandible, where the tumor first invaded the edentulous alveolar process and

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then progressed into the medullary space through the dental pores. This process, however, was not observed in patients who had received prior radiotherapy, where direct infiltration through the lingual cortex of the mandible was more common (Barttelbort and Ariyan, 1993).

Accurate assessment of the extent of invasion of the mandible is often difficult on clinical examination alone, particularly when there is no gross infiltration of the bone but the tumor approximates, is adherent to, or is directly contiguous to the mandible. In this setting, radiological evaluation is often helpful (Bernier et al., 2005; De Vicente et al., 2001). A variety of radiological studies are available, including intraoral dental films, orthopantomogram, CT scan, Denta scan, MRI, or PET scan. Early bone invasion is manifested by cortical erosion through the lingual cortex or extension of tumor through the alveolar process into the medullary space. However, negative radiological studies do not completely rule out microscopic bone invasion.

When radiological imaging studies are negative for bone invasion, a thorough examination of the tumor by inspection and palpation, under general anesthesia, is crucial. In situations where the tumor approximates the mandible without gross radiologic invasion, marginal mandibulectomy may offer a complete and oncologically safe surgical resection, securing adequate margins.

Therefore, accurate assessment for bone invasion is crucial to successful oncologic and functional outcomes. In spite of extensive literature on the selection criteria and techniques of marginal mandibulectomy (McGregor and MacDonald, 1989; McGregor and Macdonald, 1987; Muller, 1990; O'Brien et al., 2003), there is a paucity of information on the incidence of bone invasion in marginal mandibulectomy specimens and its impact on outcome. The purpose of this study was to examine the incidence of microscopic bone invasion, and the influence of bone invasion as well as positive bone margins on outcome in patients undergoing marginal mandibulectomy at a tertiary cancer care center.

2. Material and methods

The primary objective of this study was to assess the incidence of microscopic bone invasion in patients undergoing marginal mandibulectomy. The secondary objective was to report the influence of bone invasion and the incidence of positive bone margins and the impact of these on oncologic outcomes. After obtaining Institutional Review Board approval, we performed a retrospective analysis of a consecutive series of 332 previously untreated patients who underwent marginal mandibulectomy for oral cavity SCC at Memorial Sloan Kettering Cancer Center between the years 1985 and 2012. Patients receiving segmental mandibulectomies were excluded. Patients who did not have complete information in their medical records (n = 6) were also excluded. Thus, a total of 326 patients were included in the study.

Associations between variables were examined using the χ^2 test. The Kaplan–Meier method was used to analyze patient outcomes. The log-rank test and Breslow tests were used for univariate analysis. The main oncologic outcomes of interest were local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS) and disease-specific survival (DSS). LRFS and RRFS were calculated from the date of surgery to the last date of follow-up or the event date. A local event was defined as recurrence in the tumor bed, and regional event as recurrence in the neck. DSS was calculated from the date of surgery to the last date of follow-up or the event date. For DSS, an event was defined as death from recurrence or dissemination of oral cancer. Patients who died from other causes or were diagnosed with second primaries were censored at the date of the last follow-up visit. Multivariate analysis was performed using Cox regression.

3. Results

The median age of patients in the study group was 64 years (range, 32–94) and 59% were male. The majority of patients (67%) had a primary tumor of the floor of the mouth or lower alveolus.

Eighty percent of patients had early stage primary tumors (cT1-2), and approximately one-third (31%) had clinically N+ disease. Almost one-quarter (24%) of the patients in our study were edentulous (Table 1).

Overall, 49 patients (15%) had histologically confirmed bone invasion in their marginal mandibulectomy specimens. Of these, 32 had only cortical invasion, 13 had invasion of the medullary space, and the extent of bone invasion was not specified in 4. Of the 49 patients with bone invasion, 40 were dentate and 9 were edentulous. Eight patients had microscopically close or positive bone margins. Close and positive bone margins were associated with medullary bone invasion ($p < 0.001$) and primary cancers of floor of the mouth and buccal mucosa ($p = 0.032$). Thirty-one percent of patients had perineural invasion, whereas only 13% had vascular invasion (Table 2).

In our study, 44 patients had a history of dental extractions, in the vicinity of the primary tumor, compared to 282 without such a history. Bone invasion was present in 18% (n = 8), of those with the history of dental extractions, and only 1 (12.5%) of these had a positive bone margin. Five of these had only cortical invasion while

Table 1
Patient and tumor variables with and without bone involvement.

Variable		No bone involvement (n = 277)	Bone involvement (n = 49)	p-value[a]
Gender	Female	110 (39.7%)	24 (49.0%)	0.224
	Male	167 (60.3%)	25 (51.0%)	
Age	≤60	107 (38.6%)	13 (26.5%)	0.106
	>60	170 (61.4%)	36 (73.5%)	
cT	T1	84 (30.3%)	10 (20.4%)	0.440[c]
	T2	137 (49.6%)	27 (55.2%)	
	T3	28 (10.1%)	6 (12.2%)	
	T4	22 (8%)	6 (12.2%)	
	Unknown	6 (2%)		
cN	N0	190 (68.6%)	34 (69.4%)	0.951
	N1	50 (18%)	8 (16.3%)	
	N2	37 (13.4)	7 (14.3%)	
pT (n = 303)	T1	141 (51%)	13 (26.5%)	<0.001
	T2	90 (32.5%)	14 (28.6%)	
	T3/T4	24 (8.5%)	21 (42.8%)	
	T0	22 (8%)	1 (2.1%)	
pN	N0/NX	186 (67.1%)	31 (14.3%)	0.862
	N1	34 (12.3%)	7 (17.1%)	
	N2/N3	57 (20.6%)	11 (16.2%)	
Site of primary	Buccal mucosa	46 (16.6%)	4 (8.1%)	0.005[c]
	Floor of mouth	98 (35.4%)	15 (30.6%)	
	Gum	80 (28.9%)	27 (55.2%)	
	Retromolar trigone	32 (11.5%)	2 (4.1%)	
	Tongue	21 (7.6%)	1 (2.1%)	
Bone involvement	Cortical		32 (65.3%)	
	Medullary		13 (26.5%)	
	Not recorded		4 (8.1%)	
Dental status	Dentate	208 (75%)	40 (81.6)	0.322
	Edentulous	69 (25%)	9 (18.4%)	
Soft tissue margin	Negative	172 (62%)	21 (42.8%)	0.017
	Positive/Close	105 (38%)	27 (55.2%)	
	Not known	0	1 (2%)	
PNI	No	146 (52.7%)	18 (36.7%)	0.012
	Yes	55 (19.9%)	17 (34.7%)	
	Unknown	76 (27.4%)	14 (28.6%)	
Adjuvant therapy	None	175 (63.1%)	32 (65.3%)	0.775[b]
	PORT ± chemo	102 (26.9%)	17 (34.7%)	

[a] p-values do not represent unknowns.
[b] Fisher exact test used with 2×2 tables with less than 5 count in any category.
[c] >25% of cells have less than 5 count in any category – p-value is not reliable.

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