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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 (POCRT) 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=0.0), and positive soft tissue margins (p=0.05). 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.

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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.

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 (1). 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 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 (2).

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 (3, 4). 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 (5, 6, 7, 8), 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.

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.

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 (49/326 = 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 ($p=0.044$). Thirty-one percent of patients had perineural invasion, whereas only 13% had vascular invasion.

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%) amongst these had a positive

bone margin. Five of these had only cortical invasion while in 3 patients there was invasion of medullary space. One of these three had a positive margin. On the other hand, 14% (n=41), of the 282 patients without prior dental extractions, had bone invasion, and 17% (n=7) had positive margins. Amongst these 31 had cortical invasion and 10 had medullary space involvement. Only one patient with cortical invasion and 6 with medullary space invasion had positive margins. Thus, the frequency of positive margins was comparable between the two groups with or without prior extractions of teeth. Similarly, the local recurrence rate was similar, 11% (n=5) among patients with a history of extractions and 22% (n=62) among patients without a history of extractions ($p=0.105$) (Table 2).

The median follow-up for surviving patients was 55.1 months (range, 3.8 to 293.9). At the time of study analysis, 67(20.5%) patients had developed local recurrences and 39 (12%) developed regional recurrences. LRFS and RRFS at 5 years were 74.6% and 85.2% respectively. LRFS in patients with and without bone invasion was 62.8% and 76.2% respectively ($p=0.134$ Log-rank test). However, when the Breslow test was used, the difference between groups was statistically significant ($p=0.007$) (Figure 1).

None of the patients with microscopic bone invasion underwent revision segmental mandibulectomy, 27% received postoperative radiation (PORT), and 8% received postoperative chemoradiation.

Three patients with bone invasion and negative margins developed local recurrence. The primary tumor in two of these was T1 and they did not receive any PORT. They underwent further surgery, for local recurrence and remained free of further recurrence for 8 and 18 years. The third patient had a T4 primary, and received PORT, but still developed local recurrence, and died of disease within one year.

Five of the eight patients with positive bone margin received postoperative adjuvant treatment; radiotherapy alone in four, and chemoradiotherapy in one. None of the patients receiving PORT developed local/regional recurrence. Two of these died with distant failure, and the remaining two died of other causes. The single patient who received chemoradiotherapy developed local/regional recurrence and died of disease. The remaining three patients did not receive adjuvant treatment since two of them had close margins. One of these two had Fanconi anemia. The other patient was lost to follow up soon after surgery. The third patient had concurrent lung cancer and died in the postoperative period from myocardial infarction (Table 3). Bone margin status (negative vs. positive) was not predictive of outcomes among the 49 patients with bone invasion.

On multivariate analysis, when adjusting for pathological T-Stage and PNI, microscopic bone involvement was still not a predictor of LRFS. However, with this limited analysis, PNI was an independent predictor of local recurrence ($p=0.008$) with a hazard ratio of 2.391. RRFS at 5 years, for patients with no bone invasion and with bone invasion was 85.4% and 84.7% respectively, as shown in Table 4. None of the variables we examined predicted regional recurrence on univariate analysis.

The 5-year DSS for the entire cohort was 78.1% (Table 5). DSS was 79.7% for patients without bone invasion, compared to 66.0% for patients with bone invasion. The log-rank test

found similar DSS ($p=0.129$) between patients with and without bone invasion, but the Breslow test showed a significant difference between the two groups ($p=0.028$). On multivariate analysis, nodal status, early vs advanced stage, and PNI were all independent predictors of DSS, however, bone involvement was not (Figure 2; Table 5).

Discussion

There is clear consensus that marginal mandibulectomy should not be performed in patients with (a) gross destruction of the cortical bone or extension of disease to the medullary space of the mandible visible on preoperative radiological studies, (b) invasion of inferior alveolar nerve (mandibular canal) by cancer, (c) massive soft-tissue disease surrounding the lingual and lateral cortex of the mandible, or (d) the presence of tumor on the alveolar process of an irradiated edentulous mandible. A relative contraindication for marginal mandibulectomy includes reduced vertical height of the edentulous mandible. Preserving at least 10 mm of vertical height is necessary to minimize the risk of iatrogenic or pathological fracture (6). In some patients who are believed to be at risk of fracture, the stability of remaining bone may be reinforced with a titanium miniplate (7).

The practice of stripping the periosteum from the mandible at the site of tumor, before deciding between marginal and segmental mandibulectomy, is not recommended-- it violates the fundamental principle of monobloc resection of cancer (which requires adequate three-dimensional margins) and the risk of local failure by seeding or cutting through tumor (9).

The incidence of patients suitable for marginal mandibulectomy for oral cancer reported in the literature varies from 16% to 60% (10). Obviously, this depends on how stringent patient selection is prior to surgery. In our series of 1866 patients with oral cancer only 332 (18%) were considered suitable for marginal mandibulectomy. Among patients with bone invasion, the local control rate was expectedly higher after segmental resection than after marginal resection (87% vs. 75%) in one series (10). However, this difference was not statistically significant. On the other hand survival was significantly influenced by positive soft-tissue margins, but not by bone invasion or type of resection.

In our study, of the 49 patients with bone invasion, 13 (27%) had tumor extension invading the medullary space. Six of these patients did not receive PORT, 1 of whom developed local recurrence. Of the 7 who did receive PORT, 2 developed local recurrences. Of the 32 patients with only cortical erosion, 3 received radiotherapy alone (2 of whom had local recurrence), 4 received chemotherapy/radiotherapy (2 of whom had local recurrence), and 25 received no adjuvant therapy (4 of whom had local recurrence). Four patients had no information available on the extent of bone invasion. Because of the small number of patients in these groups, we were unable to determine the effect of adjuvant therapy on local control. However, it is recommended that, in cases where margins are positive or close, adjuvant therapy should be used to reduce the risk of local recurrence (11, 12, 13). It is now well established that patients with positive margins benefit by adding chemotherapy to PORT (13). Although bone invasion in general results in upstaging the tumor and is reported to be a predictive prognostic factor, a recent study showed that tumors with bone invasion limited to the cortex had a similar prognosis as those without bone invasion (14). The

findings from our study support this observation. In cases where bone invasion is not suspected preoperatively but is reported in the final pathology report, the prognosis is not worse and additional treatment is not warranted, as long as the margins of resection are clear.

We compared the incidence of bone invasion between edentulous and dentate patients, as well as the frequency of positive bone margins and local recurrence rates. There were far fewer edentulous patients than dentate patients in our study (78 edentulous patients vs 248 dentate patients). This is attributable to our preoperative selection criteria of considering vertical height of the edentulous mandible. In edentulous patients without bone invasion the LRFS was 83.9% (n=69) and for dentate patients it was 73.9% (n=208) (p=0.154). On the other hand the LRFS for edentulous and dentate patients with bone invasion and negative margins was 37.5% (n=7) and 64.7% (n=34) respectively (p=0.742). However, the frequency of positive bone margins was similar between edentulous and dentate patients (22% and 15% respectively). Surprisingly, the local recurrence rate among patients with positive bone margin was very low. Only 1 dentate patient with positive bone margin developed local recurrence; no edentulous patients with positive margins developed local recurrence. These observations underscore the finding that a microscopic positive bone margin alone is not a precipitating risk factor for local recurrence, as long as adjuvant PORT is administered. In contrast, in our study a positive soft-tissue margin or mucosal margin was highly predictive of local recurrence.

It is generally believed that patients who had dental extractions in the vicinity of the tumor before surgery have a higher risk of tumor implantation and dissemination of microscopic disease in the medullary space, and thus are more likely to be candidates for segmental rather than marginal mandibulectomy. However, such extended resections have not been shown to be particularly beneficial to patients, in terms of local control and overall survival, compared with marginal mandibulectomy. In a recent study by Yamagata et al. (14), the authors found no significant difference in tumor status, node status, local recurrence, pathologically positive lymph nodes, or distant metastasis between oral SCC patients with or without a history of dental extractions. In their study, 19 patients with oral SCC had a history of tooth extractions; 58 did not. Among patients who had undergone extractions, 15 (83.3%) had bone invasion, and only 2 had positive bone margin; among patients without extractions, 30 (60%) had bone invasion, and 7 had positive bone margins. Similar findings were observed in our study, where previous extractions did not adversely affect eventual outcomes. Nevertheless it is generally recommended to avoid extractions of teeth from tumor-bearing areas of the mandible.

In our study, 5-year DSS was twice as high among patients who did not receive any postoperative adjuvant therapy compared to those who received PORT. This paradoxical observation in DSS is attributable to patient selection for PORT. Clearly, patients who received PORT had more-advanced disease (higher T stage, higher N stage, or more-adverse pathological features), compared to those who did not (Table 6). However, 5-year LRRFS were comparable in the two groups indicating a beneficial effect of adjuvant PORT in the higher risk group.

Conclusion

Marginal mandibulectomy is an effective and oncologically sound surgical procedure to secure adequate tumor resection with preservation of the mandible in appropriately selected patients. Presence of microscopic bone invasion does not adversely influence local control even with close or positive bone margins as long as PORT is administered. Consideration should be given to adjuvant postoperative radio therapy with or without chemotherapy, on the basis of histopathologic features including the status of bone, soft-tissue and mucosal margins, and the presence and extent of nodal metastases.

Acknowledgments

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Biography

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5 year LRFS

No Bone =
76.2%

Bone
Involvement =
62.8%

Figure 1.
Local recurrence free survival for patients with and without bone invasion

5 year DSS

No Bone =
79.7%

Bone
Involvement =
66.0%

Figure 2.
Disease specific survival for patients with and without bone invasion

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 ⁺
	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 ⁺
	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	No	172(62%)	21(42.8%)	
	Yes	105(38%)	27(55.2%)	
	Not known	0	1 (2%)	
PNI	No	146(52.7%)	18(36.7%)	

Variable		No Bone Involvement (N=277)	Bone Involvement (n=49)	p-value ^a
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 [*]
	PORT ± Chemo	102 (26.9%)	17 (34.7%)	

^a . p-values do not represent unknowns

^{*} Fisher exact test used with 2×2 tables with less than 5 count in any category

⁺ >25% of cells have less than 5 count in any category – p-value is not reliable

Table 2

Margin status in patients with bone invasion

Variable		Bone Margin Negative n=41	Bone Margin Positive/Close n= 8	p=- value
Gender	Female	21 (51.2%)	3 (37.5%)	0.702
	Male	20 (48.8%)	5 (62.5%)	
Age	60	10 (24.4%)	3 (37.5%)	0.422
	>60	31 (75.6%)	5 (62.5%)	
cT	T1	9 (21.9%)	1 (12.5%)	0.657 ⁺
	T2	23 (56.1%)	4 (50%)	
	T3	4 (9.8%)	2 (25%)	
	T4	5 (12.4%)	1 (12.5%)	
cN	N0	29 (70.8%)	5 (62.5%)	0.768 ⁺
	N1	6 (14.6%)	2 (25%)	
	N2	6 (14.6%)	1 (12.5%)	
pT	T1	13(31.7%)	0(0%)	0.036 ⁺
	T2	13(31.7%)	1(12.5%)	
	T3	1(2.4%)	0(0%)	
	T4	13(31.7%)	7(87.5%)	
	Unknown	1 (2.4%)		
pN	N0	29(70.8%)	2(25%)	0.039 ⁺
	N+	12(29.2%)	6(75%)	
Site of Primary	Buccal Mucosa	2 (4.9%)	2 (25%)	0.044 ⁺
	Floor of Mouth	12 (29.2%)	3 (37.5%)	
	Lower Gum	25 (61%)	2 (25%)	
	Retromolar Trigone	2 (4.9%)	0 (0%)	
	Tongue	0 (0%)	1 (12.5%)	
Bone Involvement	Cortical	31 (75.6%)	1 (12.5%)	<0.001 [*]
	Medullary	6 (14.6%)	7 (87.5%)	
	Unknown	4 (9.8%)	0 (0%)	
Soft tissue margins	Negative	20(48.8%)	1(12.5%)	0.064 [*]
	Positive	20(48.8%)	7(87.5%)	
	Unknown	1 (2.4%)		
PNI	No	18(43.9%)	0(0%)	
	Yes	10(24.4%)	7(87.5%)	
	Unknown	13 (31.7%)	1 (12.5%)	
Adjuvant Therapy	None	29 (70.8%)	3 (37.5%)	0.106

Variable	Bone Margin Negative n=41	Bone Margin Positive/Close n= 8	p=- value
PORT ± Chemo	12 (29.2%)	5 (62.5%)	

* Fisher exact test used with 2×2 tables with less than 5 count in any category

⁺ >25% of cells have less than 5 count in any category – p-value is not reliable

Table 3

Factors impacting on local recurrence on univariate and multivariate analysis

Variable	Univariate		Multivariate	
	5yr LRFs	P-value	HR	P-Value
Gender	Male	73.4%	0.341	
	Female	76.4%		
Age	>60	72.6%	0.294	
	60	75.8%		
pT	T1	80.0%	0.016	Ref
	T2	71.0%		1.333 (0.658–2.698)
	T3/T4	60.2%		2.165 (0.933–5.023)
pN	N0/NX	75.8%	0.854	
	N1	73.0%		
	N2/N3	73.6%		
Bone Involvement	No	76.2%	0.134	Ref
	Yes	62.8%		1.160 (0.520–2.588)
PNI	No	82.4%	<0.001	Ref
	Yes	61.2%		2.391 (1.249–4.576)
Bone Invasion	Cortical	65.6%	0.722	
	Medullary	50.0%		
Site of Disease	Gum	73.5%	0.592	
	Buccal Mucosa	68.4%		
	Floor of Mouth	79.0%		
	Retromolar Trigone	75.7%		

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Variable	Univariate		Multivariate	
	5yr LRFs	P-value	HR	P-Value
Soft Tissue Margins	Tongue	77.7%		
	Negative	78.4%	0.079	
	Positive	68.5%		

Table 4

Factors impacting on disease specific survival

		Univariate	
Variable		5yr LRFS	P-value
Gender	Male	85.4%	0.527
	Female	84.7%	
Age	>60	85.8%	0.664
	60	84.9%	
pT	T1	84.4%	0.069
	T2	74.9%	
	T3/T4	96.4%	
pN	N0/NX	86.6%	0.884
	N1	82.9%	
	N2/N3	80.9%	
Bone Involvement	No	85.4%	0.794
	Yes	84.7%	
Bone Invasion	Cortical	83.7%	0.273
	Medullary	100%	
Site of Disease	Gum	86.5%	0.881
	Buccal Mucosa	86.0%	
	Floor of Mouth	81.5%	
	Retromolar Trigone	92.8%	
	Tongue	84.9%	
Soft Tissue Margins	Negative	87.7%	0.090
	Positive	81.5%	

Table 5

Factors impacting on regional recurrence on univariate analysis

Variable		5- year DSS	p= value	HR (CI)	P- value
Gender	Male	78.8%	0.662		
	Female	77.6%			
Age	>60	78.2%	0.693		
	60	77.9%			
pT	Early (T1/T2)	80.1%	<0.001	Ref	0.017
	Advanced (T3/T4)	51.0%		2.438 (1.169–5.084)	
pN	N0/NX	85.0%	<0.001	Ref	0.043
	N+	64.7%		1.984 (1.022–3.852)	
PNI	No	85.2%	<0.001	Ref	0.021
	Yes	55.1%		2.278 (1.132–4.583)	
Bone Involvement	No	79.7%	0.129	Ref	0.579
	Yes	66.0%		1.274 (0.579–2.800)	
Bone Invasion	Cortical	77.4%	0.365		
	Medullary	50.0%			
Site of Disease	Buccal Mucosa	72.1%	0.077		
	Floor of Mouth	75.4%			
Gum	Gum	81.0%			
	Retromolar Trigone	92.6%			
Tongue	Tongue	66.7%			
	Negative	83.6%	0.025		
Soft Tissue Margins	Positive	69.8%			

Table 6

Comparison of clinical and pathological variables between patients who had adjuvant therapy and those that did not.

Variable		No adjuvant Therapy (n=207)	Adjuvant Therapy (n=119)	p-value
Gender	Female	91 (43.9%)	43 (36.2%)	0.224
	Male	116 (56.1%)	76 (63.8%)	
Age	60	64 (30.9%)	56 (47%)	0.106
	>60	143 (69.1%)	63 (53%)	
pT	T1	118 (57%)	36 (30.2%)	<0.001 ⁺
	T2	53 (25.6%)	51 (42.9%)	
	T3/T4	18 (8.7%)	27 (22.7%)	
	Unknown	18 (8.7%)	5 (4.2%)	
pN	N0	186 (89.8%)	31 (26%)	<0.001
	N+	21 (10.2%)	88 (74%)	
Bone Involvement (n=49)	Cortical	25 (12.1%)	7 (5.9%)	0.026 [^]
	Medullary	6 (2.9%)	7 (5.9%)	
	Unknown	1 (0.5%)	3 (2.5%)	
Site of Disease	Buccal Mucosa	22 (10.8%)	28 (13.6%)	<0.001 ⁺
	Floor of Mouth	71 (34.2%)	42 (35.4%)	
	Gum	81 (39.1%)	26 (22.4%)	
	Retromolar Trigone	25 (12.1%)	9 (7.7%)	
	Tongue	8 (3.8%)	14 (11.9%)	

* Fisher exact test used with 2×2 tables with less than 5 count in any category

⁺ >25% of cells have less than 5 count in any category – p-value is not reliable

[^] only comparing medullary vs cortical bone involvement