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Oral Carcinoma of the Retromolar Trigone, Maxillary Alveolus and Palate

Considerations in Surgical Management

■

ACADEMIC DISSERTATION
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To My Wife Munira, & My Daughters Haya & Albandry,

For Being the Source of Love, Joy, & Happiness.

Abstract

Cancer of the oral cavity is a most devastating disease that causes a significant disfigurement of the patient with severe morbidity and mortality. It is a challenging disease in its nature and management affecting not only the function but also the cosmesis of the afflicted patients. Despite improvement in the diagnostic and management methods, the prognosis of oral cancer is still unpredictable. This series of works seeks to examine the behaviour and management of oral squamous cell carcinoma at two uncommon sites for which data is lacking; namely the retromolar trigone and the maxillary alveolus / hard palate. Additionally the thesis examines the anatomy of two important neighbouring structures which may be affected by surgical treatment; namely the maxillary artery and the marginal mandibular branch of the facial nerve. Finally the importance of the histological status of the resection margin is examined.

The cohort with squamous cell carcinoma involving the retromolar trigone consisted of 76 cases. The absolute and disease specific survivals at 5 years were 51.4% and 67.7%. In patients treated with surgery, the resection margin status predicted the overall 5- year survival (p= 0.027) with 75% of patients with negative margins surviving 5 years versus a survival of 0% of patients with involved margins. Squamous cell carcinoma of the retromolar trigone has a poor survival for early stage disease. Adequate surgical margins can improve survival.

In analysis of the cohort of 37 patients with tumors involving the maxillary alveolus and hard palate, there was a female predilection. Local recurrence was observed in ten patients with 6 failing at the primary site. The absolute and disease free survival at 5-years was 33% and 62% respectively. The 5-year disease-free survival was 82% for stage I & II and 48% for stage III and IV (p=0.056). No patient treated with radiotherapy as a single treatment modality survived 5 years. Disease free survival for patients treated with surgery, and surgery± radiotherapy, was 69% and 73% at 5 years respectively. (p=0.001). Squamous cell carcinoma of the maxillary alveolus and palate differs from other oral cancers in that the patients are relatively older with a slight female predilection. Treatment with surgery, with or without radiotherapy, appears to improve disease control.

The course of the maxillary artery relative to the lateral pterygoid muscle was dissected in 44 cadaver specimens. In the majority of the cases (30), the artery was found lateral to the lower head of the lateral pterygoid muscle (71% in males and 65% in females). The maxillary artery was found medial to the lower head of the lateral pterygoid muscle in only 14 of the cases (29% in males and 35% in females). No variations in the course of maxillary artery were noted between the two sides and between both sexes. This study shows that the lateral or superficial course of the maxillary artery relative to the lower head of the lateral pterygoid muscle to be more prevalent than the medial or deep course.

The anatomy and function of the facial nerve was studied in 133 patients undergoing neck dissections. When the neck was extended the nerve was displaced in an anterior and downwards direction with the lowest point 1.25 +/- 0.07 cm below the mandible between the posterior and anterior facial veins. When the intent was to preserve the nerve, dysfunction was seen in 16 of 101 dissections (16%).

A total of 425 patients were assessed for adequacy of the margins at the time of resection. After controlling for significant prognostic factors, involved surgical margins increased the risk of death at 5 years by 90%. The status of the surgical margin is an important predictor of outcome. The surgical margin, unlike other prognostic factors is under the direct control of the surgeon.

Keywords: oral carcinoma, maxilla, mandible, retromolar trigone, surgical margins.

Abbreviations

CT	Computed Tomography
CTX	Chemotherapy
HPV	Human papilloma virus
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
IT	Immunotherapy
MA	Maxillary artery
MMN	Marginal mandibular branch of facial nerve
MRI	Magnetic Resonance Imaging
RMT	Retromolar trigone
RT	Radiation therapy
SCC	Squamous cell carcinoma
SD	Standard Deviation
TNM	Tumor, node and metastasis classification.

Glossary of terms

Carcinoma: An epithelial derived group of malignant neoplasms.

Facial nerve: The seventh cranial nerve with numerous branches, the terminus of which supply the muscles of facial expression with motor innervation for mimetic function.

Five-year disease-free-survival: An analytic term to indicate the success of treatment protocols when comparing different groups of tumors or patients.

Hard palate: The horizontal projection of the inferior portion of the maxilla medially. Posteriorly the horizontal process of the palatine bone also joins the maxillary portion to make the hard palate. The entire bony hard plate is covered by attached mucosa and mucoperiosteum on the oral side and respiratory mucosa on the nasal side.

Lateral pterygoid muscle: A horizontal bipennate muscle responsible for protrusion of the mandible.

Marginal mandibular nerve: One of the terminal branches of the facial nerve supplying the Depressor labii inferioris, the depressor anguli oris, risorius and mentalis muscles.

Maxillary alveolus: The most inferior vertical process of the maxilla with sockets to house the maxillary teeth.

Maxillary artery: One of two terminal branches of the external carotid artery supplying the midface, masticatory muscles and overlying muscles of facial expression.

Resection margin: The limit of the resection, its perimeter, the cut edge of the removed tumor and its surrounding tissue.

Retromolar trigone: An ill-defined triangular area in the oral cavity posterior to the upper and lower third molar teeth, with the maxillary tuberosity at its apex.

Staging: The categorization of the degree of involvement or extent of a malignant tumor based on clinical examination and or radiographic or magnetic resonance examination.

TNM: Acronym for Tumor, Node and Metastasis, for classification system to aid in determining the extent of malignant disease.

List of original papers

The thesis is based on the following original articles, which are referred to in the text by the Roman numerals I - V:

I. **Binahmed A**, Nason RW, Abdoh AA, Sándor GKB (2007). *Population-based study of treatment outcomes in squamous cell carcinoma of the retromolar trigone.* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 104: 662-665. Epub 2007 Aug 29.

II. **Binahmed A**, Nason RW, Hussain A, Abdoh AA, Sándor GKB (2008). *Treatment outcomes in squamous cell carcinoma of the maxillary alveolus and palate: A population-based study*. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 105: 750-754. Epub 2008 Feb 23.

III. Hussain A, **Binahmed A**, Karim A, Sándor GKB (2008)**.** *Relationship of the maxillary artery and lateral pterygoid muscle in a caucasian sample.* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 105: 31-35. Epub 2007 Aug 29.

IV. Nason RW, **Binahmed A**, Torchia MG, Thliversis J (2007). *Clinical observations of the anatomy and function of the marginal mandibular nerve*. Int J Oral Maxillofac Surg. 36: 712-715. Epub 2007 March 27.

V. **Binahmed A**, Nason RW, Abdoh AA (2007). *The clinical significance of the positive surgical margin in oral cancer*. Oral Oncol. 43: 780-784.

Contents

1 Introduction

Cancer of the oral cavity is one of the most devastating diseases to afflict the head and neck causing significant disfigurement of the patient with severe morbidity and mortality. Oral carcinoma is a particularly challenging disease whose nature and management may have devastating effects on the function and cosmesis of patients. Despite all of the improvements in diagnostic and management methods the prognosis of oral cancer remains unpredictable. This series of works seeks to examine the behavior and management of oral squamous cell carcinoma at two uncommon sites for which data is lacking; namely the retromolar trigone and the maxillary alveolus / hard palate. The thesis also examines the anatomy of two important neighboring structures which may be affected by surgical removal of the tumor; namely the maxillary artery and the marginal mandibular branch of the facial nerve. Finally the importance of the histological status of the resection margin is examined.

Retromolar Trigone

The retromolar trigone (RMT) is an ill-defined triangular area in the oral cavity posterior to the upper and lower third molar teeth, with the maxillary tuberosity at its apex. It is a relatively uncommon site for oral squamous cell carcinoma. The prognosis for this site tends to be poor because of the advanced stage of disease at the time of presentation (Byers et al 1984, Kowalski et al 1993, Antoniados et al 2003). Squamous cell carcinoma of the RMT has been treated with primary surgery, primary radiation, and with combinations of surgery, radiotherapy, and chemotherapy with varying success (Byers et al 1984, Lo et al cell carcinoma of the RMT is relatively poor, with overall survival ranging from 26% to 80% (Byers et al 1984, Lo et al 1987, Kowalski et al 1993, Antoniados et al 2003, Ayad et al 2005).

There is no agreement on the optimal management of these tumors. Early reports recommended surgical treatment over radiotherapy. Kowalski et al (1993) described their experience with extended "commando" operations in 114 patients with or without postoperative radiation and reported a 5-year absolute survival rate of 55.3%. They concluded that adjunctive radiotherapy improved local and regional control (Kowalski et al 1993*)*. The experience reviewed by Byers et al (1984) showed a recurrence rate of 16% in patients treated with radiation therapy alone and 18% in patients treated with postoperative radiation. The 5-year absolute survival was 26% (Byers et al 1984*)*. In another report from the same institution, Lo, Fletcher & Byers (1987) reviewed experience with irradiation of the anterior faucial pillar and the RMT. The 5-year determinant survival was 83% (Lo et al 1987*)*. In a more recent study Hao et al (2006) reported a 5-year actuarial survival of 60.6% in 50 patients treated with surgery, with 24 receiving adjuvant therapy. This thesis tries to provide further information on SCC of the RMT.

Maxillary alveolus and hard palate

Another uncommon tumor, squamous cell carcinoma (SCC) of the hard palate and maxillary alveolar ridge could be considered as a single site since the two areas are adjacent anatomically and share similar clinical presentations and management. Squamous cell carcinoma of the maxillary alveolus and hard palate is relatively uncommon in Western Society (Bhansali 1961, Krolls & Hoffman 1976*)*. Petruzzelli & Mayers (1994) noted that neoplasias, both SCC and non-SCC, of the upper jaw constitute only 2% of all head and neck malignancies and 10% of oral cancers. The lesions appear to be considerably more common in India, accounting for 40% to 55% of the oropharyngeal cancers (Ramulu & Reddy 1972, Reddy 1974*).* The relatively low numbers of these tumors is the most likely reason that these lesions are often grouped and reported together with other sites such as the mandibular alveolus and soft palate or combined with salivary gland tumors. It is the feeling of this research group that these tumors should be assessed as a site independent from the mandibular alveolus and soft palate.

The anatomical characteristics of the maxillary alveolar ridge and hard palate are similar as together they form the roof of the oral cavity and the floor of the nasal cavity and maxillary sinus. Full-thickness resection of the structures involved by tumor at this site will result in oronasal and oral-antral communication, a problem unique to this site. This thesis attempts to provide further information on SCC at this site. Additionally management of maxillary tumors requires a thorough understanding of the anatomical structures in this area especially the anatomical variation of the Maxillary Artery (MA) which can be a major cause of bleeding in the surgical management of tumors at this site.

The maxillary artery

The MA arises as one of the two terminal branches of the external carotid artery behind the neck of the mandibular condyle, deep to or within the substance of the parotid gland (Allen et al 1974, Coleman & Smith 1982*).* From its origin, the course of the maxillary artery is divided into 3 parts. The first or "mandibular" part of the MA runs nearly horizontal and deep to the neck of the mandibular condyle. It is superficial to the sphenomandibular ligament during its course towards the lower border of the lower head of lateral pterygoid muscle in the infratemporal fossa. The second or "pterygoid" part of the MA runs obliquely forward either superficial or deep to the lower head of the lateral pterygoid muscle. At this site, it is embedded into the pterygoid venous plexus. Finally, the third or "pterygopalatine" part of the MA disappears from view by diving between the two heads of lateral pterygoid muscle to reach the pterygopalataine fossa via the pterygomaxillary fissure. There, it gives off several branches that accompany the corresponding branches of the maxillary nerve. The variable course of the second part of the maxillary artery has stimulated considerable discussion and a number of reports (Krizan 1960, Fisch & Pillsbury 1997, Krizan et al 1960). Lauber (1901) found only 16 arteries (8.5%) out of 200 cases to be superficial to the lower head of the lateral pterygoid muscle. However, the superficial position of the maxillary artery seemed to occur in about 54%-70% of cases in Caucasians (Lurje 1946, Krizan 1960) compared to 69% in Africans (Laskar et al 1951)

Understanding the anatomy of the human MA and its branches in the infratemporal fossa is a prerequisite for many surgical and clinical procedures. Tumors involving the cavernous sinus and the floor of the middle cranial fossa, may extend into the infratemporal fossa. Other tumors originating in the nasopharynx, the maxillary sinus, the maxilla, maxillary alveolus, hard palate, retromolar trigone and in the parotid gland can also invade the infratemporal fossa and involve the MA. This thesis tries to delineate the anatomy of the MA to facilitate surgery in this area.

Marginal mandibular branch of the facial nerve

The management of the cervical lymph nodes in treating oral cancers plays a major role in control of the disease as well as survival of the patients. It is not surprising that the presence of clinically positive lymph nodes at the time of presentation is probably the single most important factor in determining outcome and prognosis. In general patients presenting with neck node metastases do half as well as patients who present with a primary tumor only. The attempt to resect potentially involved cervical lymph nodes may cause injury to the marginal mandibular branch of the facial nerve (MMN) with functional and cosmetic deformity.

Injury to the MMN in the course of a neck dissection has been considered an acceptable outcome by some (Moffat & Ramsden 1977, Hald & Andreassen 1994) and the incidence of nerve dysfunction consequently in this context has not been reported. This is unfortunate in terms of the quality of patient care and the quality of life after resection as damage to this nerve results in a significant deformity.

The deformity is the result of interruption of the nerve fibres to the depressor anguli oris and the depressor labii inferioris that results in flattening and inversion of the ipsilateral lower lip and the inability to move the lip downward and laterally. The defect may not be apparent with the face in repose; it is certainly evident upon animation of the face. Elevation of the affected lower lip is evident when the patient smiles and the asymmetry is most obvious when the patient cries – the 'asymmetric crying facies' (Moffat & Ramsden 1977, Tulley et al 2000).

The reported incidence of MMN injury ranges from 0 to 20% following submandibular gland removal (Smith et al 1994). Knowledge of the course and anatomic relations of the MMN in the upper neck is important in order to avoid injury. The nerve is usually described relative to the lower border of the mandible and the facial vessels.

The seminal work on the surgical anatomy of the MMN is based on Dingman and Grabb's study of 100 embalmed cadaver facial halves (Dingman & Grabb 1962). They described two or more rami of this branch of the facial nerve at the level of the angle of the mandible. In 98% of specimens the nerve passed downward and forward over the surface of the posterior facial vein and more anteriorly the nerve crossed the anterior surface of the anterior facial vein in 100% of specimens (Dingman & Grabb 1962). Immediately anterior to the facial vein the branches of the mandibular ramus passed superficial, deep or on both surfaces of the facial artery. The nerve tended to be superficial to the artery (Dingman & Grabb 1962). It was found that posterior to the facial artery the marginal mandibular branch of the facial nerve ran above the inferior border of the mandible in 81% of specimens. In the other 19% the nerve or one or more of its branches ran in an arc 1 cm or less below the inferior border of the mandible (Dingman & Grabb 1962). In the region anterior to the facial artery, all branches of the MMN were above the inferior border of the mandible (Dingman & Grabb 1962).

These observations implied that incisions placed 2 cm below the lower border of the mandible would avoid injury to the nerve in all instances. Clinical observations, however, suggest that the nerve is consistently below the inferior border of the mandible. Baker & Conley noted that in individuals with lax and atrophic tissue, the nerve could be as low as 3 to4 cm below this point (Baker & Conley 1979). This thesis studies the clinical location of this nerve at the time of surgery to try to clarify the anatomic relationships of the MMN relative to other anatomic structures without the potential artefacts of embalming. This would help surgeons avoid injury to this important nerve, potentially improving the functional outcomes of ablative tumor surgery in this area.

Histological status of the resection margins

Despite the improvements in surgical and radiotherapeutic technique, intraoral squamous cell carcinoma has a relatively unfavorable prognosis with an overall five-year survival rate of 35 – 50%. The survival rate has regrettably remained virtually unchanged over the past three decades. The increase in the incidence of oral cancer further accentuates the mortality from the cancer.

Several parameters have been adapted and applied by clinicians to evaluate the prognosis of oral cancer. These parameters can be divided into epidemiological parameters which include the age, sex, race, alcohol and tobacco intake and comorbidities; clinical parameters which include the TNM classification and stage and the site of the primary tumor; and histological parameters which include the marginal status, the perineural or perivascular invasion, histopathological grading and tumor thickness and extracapsular spread.

There is no consensus as to how much normal tissue should be removed around the tumor in order to reduce the risk of local recurrence and improved survival. The ancient anatomist Galen suggested that "when excising a malignant tumor one should make accurate incisions surrounding the tumor so as not to leave a single root". This statement made two millennia ago remains one of the basic principles of oncological surgery. If a cure is to be expected for localized cancer, complete excision must be performed with adequate resection margins.

There is little doubt that a gross residual tumor will effect local control and nearly always increase mortality. Analysis of the literature shows that there is a lack of standardization and precision in defining what is a positive margin, a close margin and a clear margin. There is no prospective controlled study evaluating the effect of positive margins on local recurrence and overall disease free survival (Batsakis 1999).

Data indicates that about 15 to 30% of all oral carcinoma are inadequately excised (Loree & Strong 1990, Batsakis 1999). Some have claimed that the microscopic accuracy of inadequate surgical margin is at least 50% as judged by local recurrence (Batsakis 1999). This false negative assessment is partially due to pathological and surgical difficulties with evaluation of preoperatively irradiated tissue and submucosal extension or skip lesion areas. Another important factor is the miscommunication and lack of close cooperation between surgeons and pathologists as reported (Batsakis 1990).

This thesis also examines the hypothesis that surgical management of squamous cell carcinoma of specific sites in the oral cavity with clear margin improves the prognosis and survival of patients.

2 Review of the literature

2.1 Oral Carcinoma

Oral Carcinoma is a potentially disfiguring and devastating disease that robs the patients of their physical appearance and devastates their self esteem.

Oral cavity cancers account for about 3% of all cancers diagnosed each year in North America. The ICD codes for oral cancer include ICD9 140, 141, 143-146, 148 and 149, and ICD10 C00-06, C09, C10, C12-14. A 3% incidence is estimated to represent 27,000 newly diagnosed cases in the United States and 3,200 cases in Canada (Figure 1). In the United Kingdom in 2005 there were a total of 4,926 new cases diagnosed with oral cancer (U.K. Cancer Statistics 2009). Slightly more than 10,000 Americans and 1,000 Canadians will die of oral cancer each year (Canadian Cancer Statistics 2004, Jemal et al 2005). Studies from around the globe show that for both sexes combined cancer of the mouth and pharynx ranks sixth overall behind lung, stomach, breast, colon and rectum and cervix uteri in that order (Pisani et al 1993). The incidence ranges from a low of 1.8/100,000 per year to a high of 47/100,000 per year (Johnson et al 1977). In Europe the incidence in males ranges from 9.5 to 23.8 per 100,000 and 3.0 to 4.6 per 100,000 in females (U.K. Cancer Statistics 2009). The highest rates of oral cancer in the world are found in France (Peng et al 2000), the Indian subcontinent, Brazil (Wunsch-Filho & de Camargo 2001) and Central or Eastern Europe. The incidence of tongue cancer in Northern Finland for example is 1.0 to 1.4/100,000 (Kari et al 1997). There are also marked differences between countries in the same geographic regions (Moore et al 2000a, Moore et al 2000b).

The incidence of oral cancer increases with age in all parts of the world. In western countries, 98% of the patients are over 40 years of age. In the high prevalence areas of the world many of the patients are less than 35-years-old owing to heavy usage of various forms of tobacco. Furthermore it is now clear that in many Western countries there has been an alarming rise in the incidence of oral cancer during the past two or three decades, particularly among younger men. This trend appears to be continuing (Llewellyn et al 2001).

In industrialized countries men are affected two to three times as often as women. The most important risk factors are alcohol and tobacco consumption for intraoral cancer and sun exposure for lip cancer in those who work outdoors. The incidence of tongue and other intraoral cancer for woman can be greater or equal to that of men in high incidence areas such as India where chewing tobacco is also common among women (Shah 2003). There has been a gradual increase of the number of female patients reflected by the change in male to female ratio in Western societies. In 1996 Oliver et al (1996) reported a review of 92 cases of oral squamous cell carcinoma from 1985 – 1992 and found the male to female ratio of 1.5:1.

Figure 1. Appearance of an oral squamous cell carcinoma lesion involving the mandibular anterior alveolus.

2.1.1 Risk Factors

The recognized risk factors of oral carcinoma include tobacco, alcohol, nutritional deficiencies and exposure to viruses.

Tobacco

There is absolutely no doubt that on a global scale the use and abuse of tobacco products is a major risk factor of oral cancer. Typically 90% of men and 60% of women with oral carcinomas use tobacco (Vincent & Marchetta 1963, Johnston & Ballantyne 1977, Baker 1993). The incidence rate of oral carcinoma in smokers is six to ten times greater when compared to non-smokers. (Silverman & Griffith 1972).

There is strong evidence that active smoking is related to oral cancers. The most comprehensive source of evidence remains the International Agency for Research on Cancer or IARC (IARC 1986, Sasco et al 1986). This evidence is also summarized by the US Surgeon General's report of 1989. The attributable risk for oral cancer was the highest in males at 92% (Figure 2). Smoking intensity effects have been found to be quantitatively homogeneous across multiple case control studies of lung, bladder, oral cavity, pancreas and esophagus cancers (Lubin et al 2008). Some literature suggests that pipe and cigars are less risky for oral cancer than cigarettes (Wynder et al 1977) but a very extensive study from northern Italy shows higher risks associated with these practices for cancer of the mouth and esophagus than with cigarettes (Franceschi et al 1992). Reverse oral cigarette smoking has also been shown to carry a high risk for oral cancer development (Reddy 1974)

In Scandinavia and North America snuff or smokeless tobacco has been the source of controversy for several years now. Brown et al (Brown et al 1965) described snuff dipper's cancer in the south eastern United States where the habit of placing snuff in the lower labial sulcus was common. This was the basis of the classical description of verrucous carcinoma by Ackermann (1948) and confirmed by McCoy & Waldron (1981). A study based on combined data of the 1986 US National Mortality Follow Back Survey and the coincident National Health Interview Survey concluded that the use of smokeless tobacco either as a snuff or chewing tobacco does not increase the risk of oral cancer or of cancer of the digestive organs (Sterling et al 1992). In Scandinavia it is now becoming clear that local snuff application is not a major risk factor for oral cancer. Two recent case control studies of the oral cancer cases in Sweden have failed to show an association (Lewin et al 1998, Schildt et al 1998).

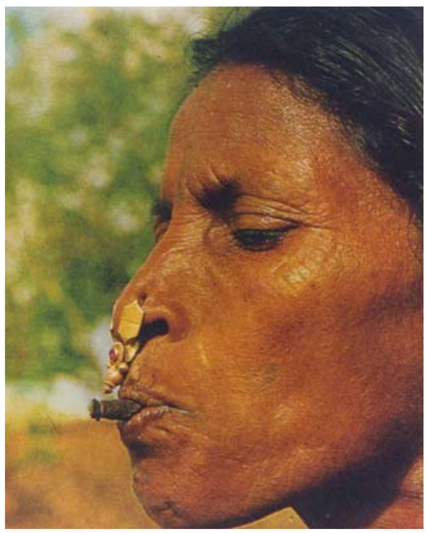

Figure 2. Reverse oral cigarette smoking is one habit thought to increase the risk of developing an oral squamous cell carcinoma.

Betel quid is a completely different form of smokeless tobacco. It is prepared from areca nut, then cured or sun dried and chopped. These pieces are placed on a leaf of the Piper betel vine and slaked lime is an essential ingredient that is added to the combination to lower the pH and accelerate the release of alkaloid from both tobacco and nut. It is a very common practice in India, Sri Lanka and Pakistan, Bangladesh, Thailand, Cambodia, Malaysian, Singapore, Indonesia, Philippine, Taiwan and China. The carcinogenicity of the betel quad mixture has been clearly established in meta-analysis of 17 published studies by Thomas and Wilson (Thomas & Wilson 1993). Gupta et al (1980) followed up 30,000 individuals over a ten-year period in three areas of India. The annual adjusted incidence of oral cancer was 23 per 100,000 among betel quad tobacco chewers compared with zero in smokers and non-chewers.

<u>Alcohol</u>

It is very difficult to separate the effects of alcohol and tobacco as most heavy alcohol consumers also use tobacco. Nevertheless some cohort and case control studies have found an increased risk of upper aerodigestive tract cancer associated with alcohol drinking in non-smokers (Kato et al 1994). The epidemiological evidence shows that all of alcoholic drinks are dangerous if heavily consumed (Schlecht et al 2001). A Finnish study showed that occupations associated with the highest incidence of oropharyngeal carcinomas were the ones with high consumption of alcohol. Exposure to solvents and possibly pesticides, engine exhaust, textile dust and leather dust may increase the risk of cancer of the mout and pharynx

(Tarvainen et al 2008). Boffetta et al (1992) have shown that the carcinogenic effect of tobacco and alcohol is through direct contact and tends to be site specific in the oral cavity. Tobacco smoking was more closely associated with carcinoma of the soft palate and alcohol was more closely associated with carcinoma of the floor of mouth and tongue.

There are several ways in which alcohol is thought to contribute to head and neck cancer by both local and systemic mechanism. The most prominent one is that ethanol increases the permeability of oral mucosa to water and many water-soluble molecules including important carcinogens. The other way that alcohol can contribute to head and neck cancer is through the immediate metabolite of ethanol, acetaldehyde, which has the capability of damaging the cells (Schlecht et al 2001). Alcoholic liver disease is common in heavy drinkers and this reduces the detoxification of active carcinogens (La Vecchia & Tavani 1998). Alcohol is also high in calories, which can suppress appetite in heavy alcohol consumers (Rennie & MacDonald 1984) and cause malnutrition, possibly contributing to oral cancer.

Nutritional Deficiencies

Nutritional deficiencies have been associated with oral cavity carcinoma. Original papers published in 1919 showed a relationship between iron deficiency and increased incidence of upper GI tract cancer in middle-aged women suffering from chronic anaemia. Several animal studies have shown that there is an epithelial cell kinetic change with iron deficiency. Some of the studies have shown an increase of turnover (Rennie & MacDonald 1984) that theoretically increases the risk of mutational error where as other studies have shown a decrease in mutational errors (Ranasinghe et al 1987). Both studies, however, have shown epithelial atrophy and increased cancer risk.

Eleven of thirteen case control studies that have examined association between fruit and vegetable consumption and oropharyngeal cancer report a meaningful inverse association (La Vecchia & Tavani 1998, Block et al 1992, Potter & Steinmetz Winn 1995, McLaughlin et al 1988).

Viruses and Other Factors

The understanding of the role of viruses as human carcinogens has progressed in the past two to three decades. Viruses contribute to the multi-step process of carcinogenesis in many human neoplasms. Human papilloma virus (HPV), especially HPV 16, is the most common type associated with not only cervical but also oral and laryngeal cancers (Yeudall 1992, Woods et al 1993, Mao 1995, Syrjänen and Surjänen 1981). In vitro studies show that high-risk HPV types can immortalize primary human oral epithelial cells. However, exposure to tobacco related chemicals were required for these cells to progress to a fully malignant phenotype (Kim et al 1993, Shin et al 1996).

Increased cancer incidence has been documented following organ transplantation. A total of 2,884 renal transplant patients in Finland with a mean follow-up of ten years were found to have an incidence o 0.8% of non cutaneous head and neck cancer (Makitie et al 2008).

2.2 Oral Carcinoma Sites

Oral cancer can occur anywhere in the oral cavity. The sites are classically divided into lip, tongue, floor of mouth, cheek, maxillary alveolus, hard palate, soft palate, mandible and retromolar trigone. Cancers of the tonsils and pharynx are not included in oral sites for the purposes of this thesis. The focus of this thesis regarding sites includes squamous cell carcinoma of the retromolar trigone and the maxillary alveolus and hard palate.

2.2.1 TNM classification

Staging of a tumor represents the categorization of the degree of involvement or extent of a malignant tumor based on clinical examination and or radiographic or magnetic resonance examination.The TNM (tumor, node and metastasis) classification was first described by Dr. Pierre Denoix at the Institute Gustaveroussy in France (International Union Against Cancer, 2002). Subsequently the International Union Against Cancer established a special committee on clinical stage classification under the leadership of Dr. Denoix and continued to develop the TNM classification. The American Joint Committee for Staging was organized in 1959 for the purpose of developing a system of clinical staging of cancer. Both organizations combined their efforts in 1988 and agreed upon the TNM classification system which was published at that time (International Union Against Cancer, 2002). There have been multiple modifications of this system since then. The most recent version was published in 2003.

The TNM system reflects the anatomical extent of the tumor. The "T" represents the size of the tumor at the primary site (T-stage) emphasizes the size or surface dimension of the tumor. A recognized deficiency of this system is the omission of tumor thickness or depth of infiltration. The "N" represents the involvement of regional cervical lymph nodes and is uniform for the classification of all malignant epithelial tumors of the upper aerodigestive tract (Figure 3). The nodal staging system takes into account the size, multiplicity, and location of metastatic nodes. The presence or absence of distant metastasis as determined by clinical exam and imaging studies, is documented as "M0" or "M1" by routine work up which may include chest radiographs, nuclear medicine scans, CT scans and MRI scans. While oral SCC tends to spread by direct extension, lymphatic spread and has a low incidence of hematologic spread, intramedullary and intradural spinal cord metastasis have been reported (Törnwall et al 2008).

Staging is important for prognostication. The stage of tumor at the time of diagnosis has been related to survival. The overall survival rates are higher in patients with stages I or II cancer are higher than those for stage III (Sargeran et al 2008).

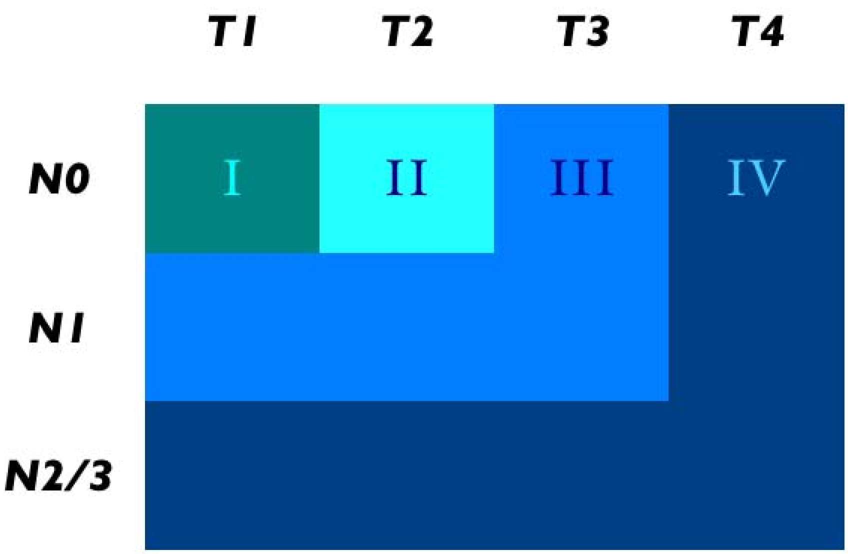

Figure 3. TNM classification relating T or tumor size and M or nodal status to large Roman numerals representing stage I to IV.

2.3 Unique aspects of the retromolar trigone, maxillary alveolus and the hard palate

The retromolar trigone and maxillary alveolus and hard palate are anatomically unique sites of oral cancer. They are poorly documented in the literature.

2.3.1 Retromolar trigone

The Retromolar trigone (RMT) is an ill-defined area posterior to the upper and lower third molar teeth. It is a triangle in shape with the maxillary tuberosity forming the apex, while the base is posterior to the mandibular third molar. The RMT is continuous laterally with the buccal mucosa, medially with the soft palate. Superiorly and inferiorly it blends with the mucoperiosteum of the alveoli (McGregor & McGregor 1986). The RMT is relatively uncommon site for oral squamous cell carcinoma (Figure 4). It is often diagnosed at advanced stage due to their oligosymptomatic early manifestations. In advanced stages pain and trismus are common due to the invasion of the mandibular nerve branches (buccal, lingual, and inferior alveolar) and muscles of mastication. Tumors of the RMT are characterized by early invasion of the mandible and the adjacent buccal mucosa and soft palate.

Figure 4. Oral squamous cell carcinoma involving the retromolar trigone.

2.3.2 Maxillary alveolus and hard palate

The anatomical characteristics of the maxillary alveolar ridge and hard palate are similar as together they form the roof of the oral cavity and the floor of the nasal cavity and maxillary sinuses. Therefore, the clinical presentation, the surgical management and reconstructive considerations, are similar for these sites. From a clinical perspective it is often difficult in advanced tumors to determine the exact epicentre (Figure 5).

Squamous cell carcinoma (SCC) of the hard palate and maxillary alveolar ridge could be considered as one site since the two areas are adjacent anatomically and share similar clinical presentations and management. These are relatively uncommon oral cancers, with a reported incidence ranging from 0.5 % to 2 % (Evan & Shah 1981, New & Hallberg 1994). Many other investigators have even considered SCC of the maxillary and mandibular alveolar ridges as similar entities (Cady & Catlin 1969, Evan & Shah 1981, Soo et al 1988, Gomez et al 2000). However, the behaviour and management of SCC involving the maxillary and mandibular alveolar ridges is different, and therefore the interpretation of their results if combined may be difficult. Other publications have not only compared and contrasted SCC of these subsites but have included other tumors of non-squamous cell origin such as salivary gland neoplasm (Chung et al 1980, Shibuya et al 1984).

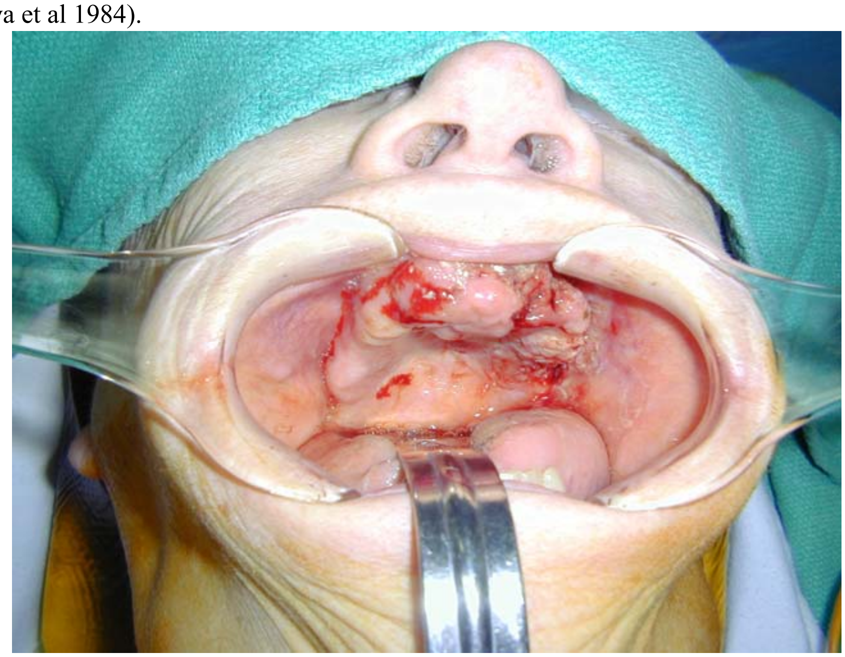

Figure 5. Oral squamous cell carcinoma lesion involving the maxillary alveolus and hard palate.

2.4 Anatomic structures at risk

While all structures of the head and neck are at risk during tumor removal, damage to blood vessel and even more so damage to cranial nerves may result in significant post operative morbidity for the patient (Dingman & Grabb 1962, Baker & Conley 1979).

2.4.1 Cranial nerve branches and blood vessels

The structures at risk during oncologic therapy of the head and neck include branches of the following nerves: cranial nerves V, VII, IX, X, XI and XII.

Iatrogenic injury is the most frequent cause of sensory disturbances in the distributions of the inferior alveolar and mental nerves (Haskell 1986, Meyer 1990, Carmichael & McGowan 1992, Ventä & Lindqvist 1998) and motor disturbances of the marginal mandibular branch of the facial nerve (Dingman & Grabb 1962).

All branches of the external carotid artery are at risk. When speaking about the resection of an oral cancer the branches at risk specifically include the facial, lingual, and maxillary arteries.

2.4.2 Marginal mandibular branch of the facial nerve

The knowledge of the course and anatomic relations of the marginal mandibular nerve of the facial nerve (MMN) in the upper neck are important in avoiding injury. The nerve is usually described as it relates to the lower border of the mandible and the facial vessels. The seminal work on the surgical anatomy of the marginal mandibular nerve is based on Dingman and Grabb's study (Dingman & Grabb 1962) of 100 embalmed cadaver facial halves. They described 2 or more rami of this branch of the facial nerve at the level of the angle of the mandible. In 98% of specimens the nerve passed downward and forward over the surface of the posterior facial vein and more anteriorly the nerve crossed the anterior surface of the anterior facial vein in 100% of specimens. Immediately anterior to the facial vein the branches of the mandibular ramus passed superficial, deep, or on both surfaces of the facial artery. They tended to be superficial to the artery. They found that posterior to the facial artery the mandibular ramus ran above the inferior border of the mandible in 81% of their specimens and in the other 19% the nerve or one or more of its branches ran in an arc one cm or less below the inferior border of the mandible. Anterior to the facial artery all branches were above the inferior border of the mandible. Dingman & Grabb (1962) made observations and other cadaver dissections (Ziarah et al 1981) imply that incisions placed 2 centimeters below the lower border of the mandible will avoid injury to the nerve in all instances. Clinical observations (Baker & Conley 1979, Nelson et al 1979) suggest that the nerve is consistently below the inferior border of the mandible. Baker and Conley (1979) noted that in individuals with lax and atrophic tissue, the nerve could be as low as 3 to 4 cm below this point.

The MMN is particularly at risk when operating in the upper neck. Injury to the MNN results in a significant cosmetic deformity. The deformity is caused by interruption of nerve fibres to the depressor anguli oris and the depressor labii inferioris that results in flattening and inversion of the ipsilateral lower lip and the inability to move the lip downward and laterally. The defect may not be apparent with the face in repose. Elevation of the affected lower lip is evident when the patient smiles and the asymmetry is most obvious when the patient cries “the asymmetric crying facies" (Moffat & Ramsden 1977, Tulley et al 2000). The reported incidence of marginal mandibular nerve injury ranges from 0 to 20% following submandibular gland removal (Smith et al 1993, Hald & Andreassen 1994, Ichimura et al 1997). Injury to the marginal mandibular nerve in the course of a neck dissection has been considered an acceptable outcome (Hald & Andreassen 1994, Moffat & Ramsden 1977) and the incidence of nerve dysfunction in this context is not reported.

2.4.3 Maxillary artery and its branches

The maxillary artery arises as one of the two terminal branches of the external carotid artery behind the neck of the mandibular condyle, deep to or within the substance of the parotid gland (Fisch 1978, Coleman & Smith 1982). From its origin, the course of the maxillary artery is divided into three parts: The first or “mandibular” part runs nearly horizontal and deep to the neck of the mandibular condyle, and superficial to the sphenomandibular ligament during its course to the lower border of the lower head of lateral pterygoid muscle in the infratemporal fossa. The second or “pterygoid” part runs obliquely forward either superficial or deep to the lower head of the lateral pterygoid muscle. At this site, it is embedded into the pterygoid venous plexus. Finally, the third or “pterygopalatine” part disappears from view by diving between the two heads of lateral pterygoid muscle to reach the pterygopalataine fossa via the pterygomaxillary fissure. There, it gives off several branches that accompany the corresponding branches of maxillary nerve.

The highly variable course of the second part of maxillary artery has stimulated a considerable number of reports (Krizan 1960, Fisch & Pillsbury 1997). Lauber found only 16 arteries (8.5%) out of 200 cases superficial to the lower head of lateral pterygoid muscle. However, the superficial position of the maxillary artery seems to occur in about 54 to 70% of the cases in Caucasians (Thompson 1891, Lurje 1946, Laskar et al 1951, Krizan 1960, Fisch 1978, Fisch 1982) and in 69% in Africans (Laskar et al 1951). Adachi (1928) stated that the superficial position of the second part of MA occurs with highest frequency in the Japanese population, and referred to it as a “racial difference”. In support of this idea, Laskar and co-workers (Laskar et al 1951) found the artery deep to the muscle in 46% of 147 cases in Caucasians, and in 31% of 61 cases in Africans, and hence, coined the term “racial blood vessel”.

2.5 Modalities of oral cancer treatment

Oral cancer therapy may consist of surgical resection, radiation therapy, chemotherapy and immunotherapy.

2.5.1 Surgical oncology

Surgical oncology is the treatment of an oral cancer primarily with surgical resection. Occasionally surgery may also be required to manage a recurrence following primary radiation therapy or as a salvage surgery (Meier et al 1984).

2.5.1.1 Surgical resection

Surgical resection of a tumor involves excising all clinical tumor with a surrounding margin of normal tissue it should bear in mind that tumors presented in three dimensions when treating it. The balance of curing the disease and maintaining the functional and cosmetic aspects is like walking a fine line that requires full knowledge of the clinical anatomy of the area (Baker 1993). Surgery still plays the major treatment modality in most of oral cancer. Surgical resection provides a cost effective and expeditious treatment for this kind of cancer (McCarty & Million 1994). Surgery also has fewer side effects than other modalities of treatments (Jacobs et al 1993), although the late stages of oral cancer still require other modalities of treatment in conjunction with the surgical resection.

There are several approaches to the oral cavity that are used in treating oral cancer. The simplest approach is the per-oral approach that is used in early stage and accessible tumors (Figures 6 and 7). Other more invasive approaches include the check flap with or with out mandibulotomy to have more access to advanced tumors or tumors seated in the posterior aspect of the oral cavity (Baker 1993). More advanced tumors of the maxilla may require a Weber-Ferguson approach to have a full access for resection (McCarty & Million 1994).

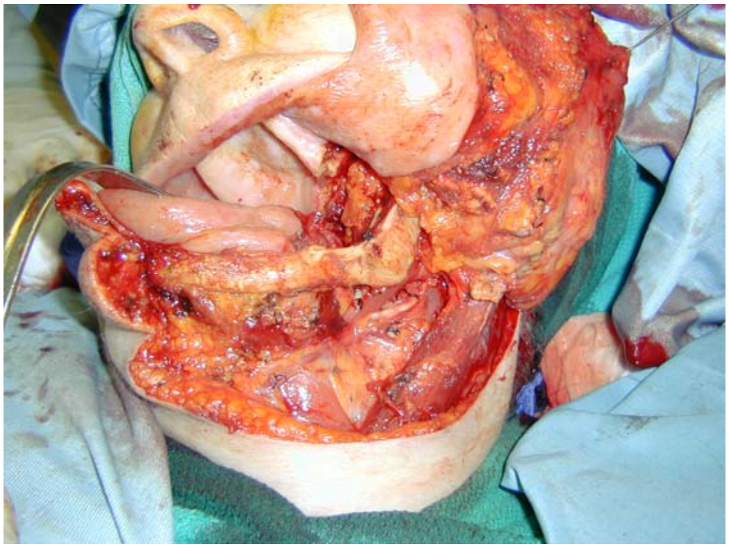

Figure 6. Partial mandibulectomy and neck dissection to remove lesion of retromolar trigone.

Figure 7. Neck dissection specimen and mandibulectomy specimens along with margins to check for completeness of tumor removal.

2.5.1.2 Radiation therapy

Radiation therapy (RT) can be used either as a primary modality but more commonly today as an adjunctive treatment to achieve tumor control. Postoperative radiation therapy has an established role in the management of advanced squamous cell carcinoma of the head and neck. Amdur et al (1989) in 1989 and Jacobs et al (1993) reported that the local failure in patients that were treated with surgery with positive margins followed by adjuvant radiation therapy was higher than the patients with negative margins. One important factor influencing local control in patients with positive margins is the dose of postoperative radiotherapy. Zelefsky et al (1993) reported a seven-year local control of 92% in patients who received greater than 60 Gray compared with 44% in patients who received less than 60 Gray showing improved survival.

Beitler et al (1998) reported a study of 29 patients with microscopically close or positive margins after curative surgery treated with postoperative external beam radiotherapy to a median dose of 60 Gray followed by iodine-125 permanent implant designed to deliver an accumulative life-time dose of 120 to 160 Gray to the high risk target volume. This treatment strategy resulted in 92% two-year local control.

2.5.1.3 Chemotherapy and immunotherapy

Chemotherapy (CTX) and immunotherapy (IT) are generally adjunctive treatments useful in the management of oral cancer. Their role in management of oral cancer is still in the investigation phase, though CT and IT are used in other head and neck cancers.

2.6 Surgical margins

There is no consensus as to how much normal tissue should be removed around a particular tumor in order to reduce the risk of local recurrence and improve the survival. Galen suggested that "when excising a malignant tumor one should make accurate incisions surrounding the tumor so as not to leave a single root" (McCarty & Million 1994). This statement, made two millennia ago, is still one of the basic principles of oncological surgery. If a cure is to be expected for localized cancer, complete excision must be performed with adequate resection margins.

2.6.1 Margin Classification

The definition of positive close and negative surgical margin lacks standardization and certainly precision (Figure 8).

In a recent study by Meier et al (2005) administered a questionnaire to members of the American Head and Neck Society. A total of 1500 surveys were mailed and a total of 476 completed surveys were received. In the definition of clear margin 46% defined a clear margin as more than 5 mm on microscopic examination from the edge of the tumor on permanent section. The second most common response given was that the margin varied according to the clinical situation or that multiple criteria were used. Twelve percent reported that a clear margin was a margin that did not have an ink stain on the tumor edge. Participants were also asked what they considered to be a close margin: 69% defined close as a margin within 5 mm of the tumor on microscopic examination; 21% defined a closed margin as less than one high powered field; and 9% defined the closed margin with other criteria. When the surgeons were asked if they considered carcinoma in situ or dysplasia at the margin as a positive margin, 83% considered carcinoma in situ as a positive margin while 76% did not consider dysplasia as a positive margin. This study illustrated the lack of standardization in definition of the margin status.

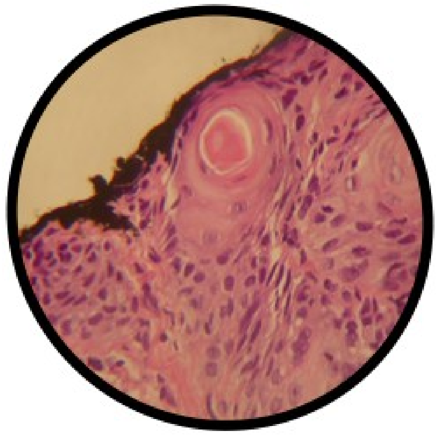

Figure 8. Photomicrograph showing black ink visible on the surgical margin with invasive squamous cell carcinoma immediately adjacent to the ink. This illustrates a positive surgical margin. Hematoxylin and eosin section 200x magnification.

2.6.2 Frozen sections

Intraoperative frozen section analysis of margins is widely employed to assist in complete tumor resection. The technique of frozen section preparation dates to 1818 and has been credited to the work of Deremier (Krubhaar 1937). It has improved over the years. The accuracy of frozen section diagnosis compared with permanent control in head and neck surgery has consistently been reported between 95% and 99%.

Several publications have assessed the accuracy of frozen section margins relative to the adequacy of tumor resection through measurements of local control and disease free survival. Byers et al (1978) reviewed a selected group of 216 patients undergoing surgical treatment of squamous cell carcinoma of the head and neck. Twenty-three percent of this sample size then underwent an intraoperative margin revision due to a positive frozen section study. The local recurrence rate for free margin was 14%, revised margin was 20%, and for the positive margin 80%. In his study Byers et al support the use of frozen section margin evaluation in all cases of squamous cell carcinoma of the head and neck except T4 lesions. Byers et al reported that there is a poor local control rate in these tumors despite the margin status. Ord et al (1997) in a study of 49 patients with oral SCC noted an accuracy rate for frozen section margins of 99% compared with permanent section of the same tissue. However, 70% of patients with a positive final margin on the resection specimen were not detected by frozen section evaluation. A positive final margin included resection margins containing dysplasia, carcinoma in situ, infiltrating carcinoma and margins within 5 mm of the carcinoma. There are two forms of error that can occur in frozen section margin evaluation. The first one is interpretive and the second is the sampling. Interpretive error denotes a failure to correctly identify the tissue present on frozen section slides. The sampling error is mainly related to the surgeon sampling a non-representative tissue and this has been reported to be mainly at the deep margin (Byers et al 1978). New techniques need to be employed to advance the sampling and intra-operative assessment of the deep margin of squamous cell carcinoma of the oral cavity.

2.6.3 Resection planning

The initial margins are determined by the planned extent of the resection which is dependent on the surgical staging and the balance between achieving disease free status and the sacrifice of life sustaining structures and the ultimate morbidity of their long-term loss (McCarty & Million 1994). The optimal resection margin should not compromise local control from an inadequate resection or cause unnecessary functional morbidity from too much resection. There is no single definition for an adequate clinical resection margin (Byers et al 1978). This needs to be individualized with consideration of the patient and tumor related variables. The complexity of defining the adequate clinical margin is further compounded by the fact that certain variables, such as tumor thickness or the pattern of invasion at the tumor host interface may not be known until a final pathology report is rendered. Recurrence in the presence of a clear margin may result from many reasons such as the presence of residual tumor not identified by the pathologist (sampling error) or a margin of pre-conditioned epithelium or field change around the tumor.

The positive association of margin status with various tumor related factors indicates that negative margins are harder to achieve with large tumor loads, proximity to mandible and a posterior location in the oral cavity. In a similar fashion the ability to achieve a wide negative margin was associated with the use of composite resection and segmental mandibulectomy. Similarly, it would make sense that a wider margin would be necessary to achieve the goal of a histologically negative margin in a tumor that invades deeply as nests and cords of cells as opposed to a tumor with a broad and flat pushing margin (McMahon et al 2003). The presence of tumor at the resection margin is recognized as an indicator of more aggressive disease (Kademani et al 2005).

2.6.4 Post Removal Changes

The measured margins of oral cavity tumors shrink from when they are first removed *in situ* by the surgeon to the final measurement on the microscope slide by the pathologist. This shrinkage can range from 30 to 50%. Beaumont et al (1992) reported on the significant changes in the longitudinal diameter of whole SCC specimens from the *in situ* fresh states to the fixed state. The most significant alteration was in the measured diameter of the tumor with a mean shrinkage of 4.28 mm from the fresh to the fixed state. In this study there was a reduction of 46% from the planned surgical margin before resection to the time of microscopic clearance in the surgical pathology laboratory. Johnson et al (1997) reported a study on mongrel dog oral mucosa. They showed shrinkage rate in the labial buccal mucosa of 47.3% while the tongue shrinkage rate varied between 30.7% for the mucosal margin and 34.5% for the deep tongue margin. The greatest proportion of shrinkage occurred immediately upon resection (Johnson et al 1997).

2.6.5 Effect of Margin on Prognosis

Loree and Strong (1990) analyzed the significance of positive margins on survival in a large group of patients with a primary oral cavity carcinoma. A total of 398 patients were studied. The overall local recurrence rate in the entire positive margin group was twice the negative margin group, 36% versus 18% respectively. A positive margin also adversely affects survival. The five-year survival rate of the positive and negative margin groups were 52.7% and 60% respectively. In this study there was no improvement in overall survival or local control with the use of adjuvant radiotherapy.

In a study of 270 patients with tumors from a variety of oral cavity, pharyngeal and laryngeal sites Chen et al (1987) found the local recurrence rate in patients with negative margins to be 17%. For the 35 patients with positive margins in this study the local recurrence rate for microinvasive carcinoma, in situ, and close margin were 55%, 50% and 45% respectively. The proportion of patients surviving five years was significantly greater among those with negative margins.

In a recent study by Sutton et al (2003) from the Department of Maxillofacial Surgery in Liverpool, 200 consecutive patients undergoing primary surgery for previously untreated oral and oropharyngeal squamous cell carcinoma were evaluated. Of the 200 patients, 107 (53.5%) had a clear margin, 42% had a close margin and 4.5% had involved margin. They defined the clear margin as no evidence of tumor within 5 mm of the margin on histological assessment of formalin fixed tissue. They defined the close margin as tumor within 5 mm of the margin but with no evidence of tumor at the margin. They defined the involved margin as evidence of frank tumor at the margin. Their follow-up data showed that close surgical resection margins were associated with a shorter disease free and disease specific survival. At five years 78% of patients were alive and well or dead and free of disease, compared to 47% of those with close margins and 11% of those with involved margins. Patients with close surgical margins were at significantly greater risk of developing local recurrence (clear 12%, close 33% and involved 55%) or regional recurrence (clear 4%, close 10% and involved 22%). Their five year overall survival was 54% for patients with clear margin, 26% for patients with close margin and none of the involved margins survived five years. In their multivariate Cox regression analysis the relative risk of death associated with involved margin was 11.6, close margin was 2.66 and positive cervical nodes was 2.15.

McMahon et al (2003) reported their findings in two independent groups of patients. Two hundred and thirty-seven patients with oral and oropharyngeal carcinoma were treated in Sydney, Australia and 95 patients were treated in Lanarkshire, England. Using a univariate analysis a number of factors significantly predict the local recurrence in each group. In the Sydney group the condition of margins was one of them. While in the Lanarkshire group the status of the surgical margin did not predict the local recurrence with a univariate analysis. However, using a multivariate analysis only the observation of perineural invasion at the primary tumor site was an independent predictor of local recurrence. This applied to both groups of patients. When disease specific survival was studied on the univariate analysis the condition of margins was a significant prognostic indicator of the five-year disease specific survival in both groups. However, on multiple regression analysis only the presence and extent of regional nodal involvement independently influenced the disease specific survival. Their study concluded that for most patients who have a close or involved margin the biology of the disease influences the subsequent course irrespective of the width of clearance of tumor. This area of oral SCC margins requires further research and clarification.

2.7 Statistical Methods

The use of simple methods of statistical analysis are routine in studies involving basic research. These methods include descriptive statistics such as the mean and its standard deviation for continuous variables, and percentage and sample size for categorical variables. Tests such as Chi-Square are also useful for categorical variables whereas t-tests are useful for continuous variables.

Kaplan-Meier curves comparing time-to success (survival) probabilities between the two study groups, using the Log-rank test, are more complex but aid in evaluating populations where survival from a disease is in question (Kaplan & Meier, 1958). A multivariate Cox's proportional hazard model may be used to test the hypothesis of increased hazard or risk of death after controlling for potentially confounding variables, such as age and tumor stage (Cox, 1972). In addition, this model produces adjusted hazard ratios (HR) and the estimated adjusted probabilities of overall survival for each predictor in a particular model (Spruance et al 2004).

3 Aims of the study

The purpose of this study is to expand the body of knowledge associated with the surgical treatment of oral squamous cell carcinoma. Therefore the specific aims of the study were:

1. To determine the treatment outcomes of squamous cell carcinoma of the retromolar trigone using a population-based study.

2. To determine the treatment outcomes of squamous cell carcinoma of the maxillary alveolus and palate using a population-based study.

3. To describe the relationship of the maxillary artery and the lateral pterygoid muscle in a Caucasian sample and how this could impact on oral cancer care.

4. To observe the anatomy and function of the marginal mandibular branch of the facial nerve as it pertains to the surgical management of oral cancer.

5. To test the significance of the positive surgical margin in oral cancer management.

4 Methods and Materials

4.1 Subjects

This research project was performed involving a total of 715 subjects in whom oral cancer sites or related anatomy were the focuses of these studies. The work was divided into five studies. The numbers of subjects, with their demographic data, are listed in Table 1.

Table 1. Number, gender and mean age with range of the subjects participating in the five studies.

Study	n (Male/Female)	Age x (range)
I (Patients)	76 (56/20)	67.2 (56-78)
II (Patients)	37 (12/25)	72.8 (59-85)
III (Cadavers)	44 (21/23)	69.6 (58-74)
IV (Patients)	133 (78/48)	54.3(37-71)
V (Patients)	425 (250/175)	63.6(51-76)

n= number of male or female subjects. x=mean.

The protocols to conduct these five studies and to review patient records were approved by the research ethics committees and by the Department of Anatomy, University of Manitoba, Winnipeg, Canada, as part of a protocol entitled “A Quality Management Program for Head and Neck Oncology” (Protocol Reference Number: H2005:071) prior to the commencement of the studies.

4.2 Methods

4.2.1 Study I Retromolar Trigone Carcinoma

In study I, a total of 88 charts of patients registered with squamous cell carcinoma of the retromolar trigone in the Province of Manitoba from January 1975 to January 2004 were evaluated. Twelve patients were excluded from the study. This was because of incorrect site coding (n=3), insufficient clinical data (n=6), or pathology report absent or inconsistent with squamous cell carcinoma (n=3). Seventy-six cases of biopsy-proven previously untreated squamous cell carcinoma of the retromolar trigone were identified. One patient presented with bilateral disease 10 years apart. This patient was considered as two distinct cases.

Tumor staging was done using clinical data recorded at the time of initial assessment of each patient according to the TNM (tumor, node and metastasis) classification system of the International Union Against Cancer, 2002. After appropriate merges and data transformation, statistical analysis was done using SPSS software (SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and percent (%) and sample size (n) for categorical variables. The comparison between the study groups was done for baseline characteristics using Pearson chi-square, with continuity correction when appropriate, or Fisher's exact test for categorical variables and t-test or Mann-Whitney U-test for continuous variables. Kaplan-Meier curves comparing time-to success (survival) probabilities between the two study groups, using the Log-rank test, were used.

4.2.2 Study II Carcinoma of the Maxillary Alveolus and Hard Palate

In study II, the records of 62 patients diagnosed with SCC of the upper jaw and registered in the Province of Manitoba from January 1975 to January 2004 were evaluated. Patients were excluded for the following reasons: incorrect site coding (n=6), insufficient clinical data (n=2), other pathology (n=16), and patients seen in consultation only (n=1). There were 37 cases of biopsy-proven and previously untreated SCC of the maxillary alveolus and hard palate (Figure 9). Staging was done using clinical data recorded at the time of the initial assessment of each patient according to the TNM (tumor, node, and metastasis) classification system of the International Union Against Cancer, 2002.

After appropriate merges and data transformation, statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables, percentage (%), and sample size (n) for categorical variables. The comparison between the study groups was done according to baseline characteristics using the Pearson chi-square test with continuous correction when appropriate, Fisher's exact test for categorical variables, and t-tests or Mann-Whitney U-test for continuous variables. Kaplan-Meier curves were used to compare time-to success or survival probabilities between the different study groups using the Log-rank test.

4.2.3 Study III Maxillary Artery

Study III is based on investigations in 44 cadavers (21 males and 23 females) that were embalmed and preserved in 2 % formalin in the gross anatomy dissection laboratory at the University of Manitoba. All specimens were Caucasians of known age and sex.

The maxillary arteries were dissected bilaterally using a lateral infratemporal approach. The covering soft tissues including the skin, fascial layers, superficial portion of parotid gland, masseter and temporalis muscles were removed. The lateral surface of the ramus of the mandible was exposed along with the external carotid artery and the origin of the maxillary artery. This approach also exposed the mandibular condyles. Using an angled oscillating saw (Stryker, Kalamazoo, Michigan, USA), the zygomatic arches were removed and the mandibles were osteotomized at the neck of the condyles and at the symphysis menti. The attachment of the lateral pterygoid muscle to the pterygoid fovea and the tempromandibular joint was preserved. The mandible was then removed from its muscular attachments including the medial pterygoid, anterior belly of digastric, mylohyoid, geniohyoid, and genioglossus muscles without damaging any underlying tissues (Figure 10). These procedures were also carried out on the contra lateral side.

Careful dissection of the first and second parts of maxillary artery was performed so that the intimate relation of the second part of maxillary artery to the lower head of lateral pterygoid could be visualized. The superficial (Figure 10) or deep location (Figure 11) of the second part of the maxillary artery to the lower head of the lateral pterygoid muscle was recorded in every specimen. This relationship and any variations in symmetry were checked and documented. Photographs were taken using a digital camera (Nikon, Coolpix 4500, Tokyo, Japan). The information collected was statistically analyzed using the two-tailed binomial test assuming a 50% chance that the maxillary artery will be superficial or deep to the inferior head of the lateral pterygoid muscle.

4.2.4 Study IV Marginal Mandibular Nerve

In study IV, clinical observation of the anatomy and function of the marginal mandibular nerve were recorded in 133 neck dissections in 121patients. There were 78 males and 48 females with a mean age of 54.31±17.0 years. The neck dissections were done for squamous cell carcinoma (n=93) thyroid cancer (n=21), salivary gland malignancy (n=9), melanoma (n=8), angiosarcoma (n=1), and Levoise-Bensaud syndrome (n=1). The neck dissections were classified as comprehensive in 72 necks, selective in 59, and extended in 2. Level I nodes were removed in 109(83%) of the dissections. Twenty-five patients had received radiotherapy prior to the neck dissection.

All patients were positioned with a roll under the shoulders to maintain extension of the neck. Skin incisions in the upper neck were placed in skin creases 2 to 4 cm below the lower border of the mandible. In general skin flaps were elevated with sharp dissection in a sub-platysmal plane. When Level I was dissected an attempt was made to identify the marginal mandibular nerve using standard landmarks. This generally involved the observation of the nerve coursing superficial to the anterior facial vein. The distance from the lower border of the mandible to the lowest point of the nerve in the neck was measured. The relationship of the lowest point of the marginal mandibular nerve to the anterior facial vein and posterior facial vein (anterior division of retromandibular vein) was noted. These measurements and relationships were recorded with the head in a neutral position, and in an extended position with downward traction on the investing layer of the deep cervical fascia.

The functional status of the marginal mandibular nerve was recorded at the time of each postoperative visit. The patients were generally followed at intervals of 2 to 3 months. The average length of follow-up was 661.18 days (range: 7-1832 days; median: 541 days). Statistical analysis was performed with a Student's t-test, Chi-Square, or multivariate analysis where appropriate.

4.2.5 Study V Histologic Resection Margins

In study V, an historical cohort of 707 patients with squamous cell carcinoma of the oral cavity from the cancer registry of the Province of Manitoba, Canada from January 1975 to 2005 was examined. After excluding patients with incomplete records (n=34), seen in consultation only or treated with palliative intent (n=69), treated with radiotherapy as a single treatment modality (n=179) there were 425 cases of biopsy proven and previously untreated squamous cell carcinoma of the oral cavity managed with surgery with or without adjunctive radiotherapy. Pathology reports were reviewed for the status of the resection margin. The presence of tumor at the inked resection margin was considered as a positive margin. Tumor identified within 2 mm of the inked resection margin was recorded as a close margin. Tumors were staged using the TNM classification (International Union Against Cancer, 2002). Categorical data was evaluated using Pearson chi-square, with continuity correction when appropriate, or Fisher's exact test. A t-test or Mann-Whitney U-test was used for continuous variables. For survival analysis Kaplan-Meier curves and log-rank test for comparing sub-groups was used A multivariate Cox's proportional hazard model was used to test the hypothesis of increased hazard or risk of death with close and involved margins after controlling for potentially confounding variables, such as age, tumor stage, etc., was done. In addition, this model produced the adjusted hazard ratios (HR) and the estimated adjusted probabilities of overall survival for each predictor in the model.

4.2.6 Statistics

In studies I and II, descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and percent (%) and sample size (n) for categorical variables. The comparison between the study groups was done for baseline characteristics using Pearson chi-square, with continuity correction when appropriate, or Fisher's exact test for categorical variables and t-test or Mann-Whitney U-test for continuous variables. Kaplan-Meier curves comparing time-to success (survival) probabilities between the two study groups, using the Log-rank test, were used.

In study III, the information collected was statistically analyzed using the two- tailed binomial test assuming a 50% chance that the maxillary artery will be superficial or deep to the inferior head of the lateral pterygoid muscle.

In study IV, the statistical analysis was performed using Student's t-test, Chi-Square, or multivariate analysis where appropriate.

In study V, categorical data was evaluated using Pearson Chi-Square, with continuity correction when appropriate, or Fisher's exact test. A t-test or Mann-Whitney U-test was used for continuous variables. For survival analysis Kaplan-Meier curves and log-rank test for comparing sub-groups was used. A multivariate Cox's proportional hazard model was used to test the hypothesis of increased hazard or risk of death with close and involved margins after controlling for potentially confounding variables, such as age and tumor stage, for example, was done. In addition, this model produced the adjusted hazard ratios (HR) and the estimated adjusted probabilities of overall survival for each predictor in the model.

5 Results

5.1 Retromolar Trigone Carcinoma

There were 56 men and 20 women, with a mean age of 67.22±10.3 years. Tobacco or alcohol use, or a combination of both was documented in 66 (86%) patients (Table 2).

Table 2. Demographics of patients with squamous cell carcinoma of retromolar trigone.

Parameter	Number
Male	56 (74%)
Female	20 (26%)
Age at presentation	67.26 +/-10.3 years
Tobacco and / or alcohol use	66 (86%)

Diabetes, hypertension and ischemic heart disease were the most common comorbidities recorded. Twenty-three patients had 34 second primary tumors, of which 62% were synchronous and 55% involved the upper aerodigestive tract.

Eight patients had Stage I lesions, while 25, 12, and 29 patients had Stage II, III, and IV disease respectively (Table 3). Two patients did not undergo staging. Twenty-eight patients (36%) had clinically positive nodes at the time of presentation.

Table 3. Stage of squamous cell carcinoma of retromolar trigone at diagnosis and survival.

Stage of Disease	Number of Patients At Diagnosis	Five Year Survival
I	8	75%
II	25	57%
III	12	56%
IV	29	38%

Twelve patients were treated with a palliative intent. Surgical treatment was used as the primary modality in 20 (26%) patients. Fifteen patients received postoperative radiotherapy. Radiotherapy was used with curative intent in 29 patients (39.5%). Three of these patients had a neck dissection for persistent disease.

Intraoral excision of the primary tumor was performed in 5 patients, while the reminder required a cheek flap for exposure. Thirty-two patients underwent mandibular resection, either a marginal resection (n=10) or segmental mandibulectomy (n=22). Primary closure was possible in 11 patients. Margins on permanent section were clear in 18 patients, close (within 2 mm) in 8 patients, and involved in 7 patients. Radiation therapy as a primary treatment modality or as adjunctive treatment was delivered by conventional fractionation at a dose ranging from 4350 to 6600 cGy.

Twenty-nine patients were managed with neck dissection alone. Ten patients were treated with neck dissection and adjunctive radiotherapy. Thirty-seven patients were treated with radiation therapy alone.

Twenty-eight patients failed treatment, 18 (64%) at the primary site, 3 (10.7%) in the neck, 2 (7%) at the primary site and in the neck. Four patients had distant metastasis, and the site of failure was not documented in one patient.

The overall median survival time was greater than 60 months and 51.4% of the patients survived the 5-years period. When disease specific survival was considered 67.7% of the patients survived the 5-years period and median survival time was still above 60 months. The median disease free survival was 60 months and 40.3% of the patients survived 5 years.

There was no statistically significant difference between stage of disease and overall survival. Five-year overall survival rates were 75%, 57%, 56%, and 38% for Stage I, II, III and IV respectively, (p=0.2230) (Table 3). Five-year overall survival rates for patients with N0 and N+ neck disease were 55% and 47.5% respectively (p=0.5712). The 5-year overall survival by treatment modality for patients treated with surgery alone was 64%, surgery and radiotherapy 57%, and 45% when radiation was elected as a single treatment modality (p=0.1260). The 5-year overall survival for patients with clear, close (within 2 mm) or involved surgical margins was 68%, 83%, and 0.0%, respectively, (p=0.0270).

5.2 Carcinoma of the hard palate and maxillary alveolus

The tumor epicenter was found to involve the maxillary alveolar ridge in 26 patients and the hard palate in the remaining 11 patients (Figure 9). There were 12 males and 25 females, with a mean age of 72.8 years (SD12.1). Tobacco, alcohol consumption, or a combination of both was documented in 19 (50%) patients. One patient was a reverse cigarette smoker. Diabetes, hypertension, and ischemic heart disease were the most common comorbidities recorded. Eight of the patients had a total of 11second primary tumors, of which 42% were synchronous and involved the upper aerodigestive tract. Fourteen patients (38%) had pain as the major presenting symptom. Six patients had stage I lesions, 9 stage II, 4 stage III, and 15 patients stage IV. Three patients could not be staged. Seven patients (19%) had clinically positive nodes at the time of presentation (Table 4).

Table 4. Stage of disease at time of presentation. Three patients were not staged.

Stage of disease	Number of patients
Stage I	6
Stage II	9
Stage III	4
Stage IV	15

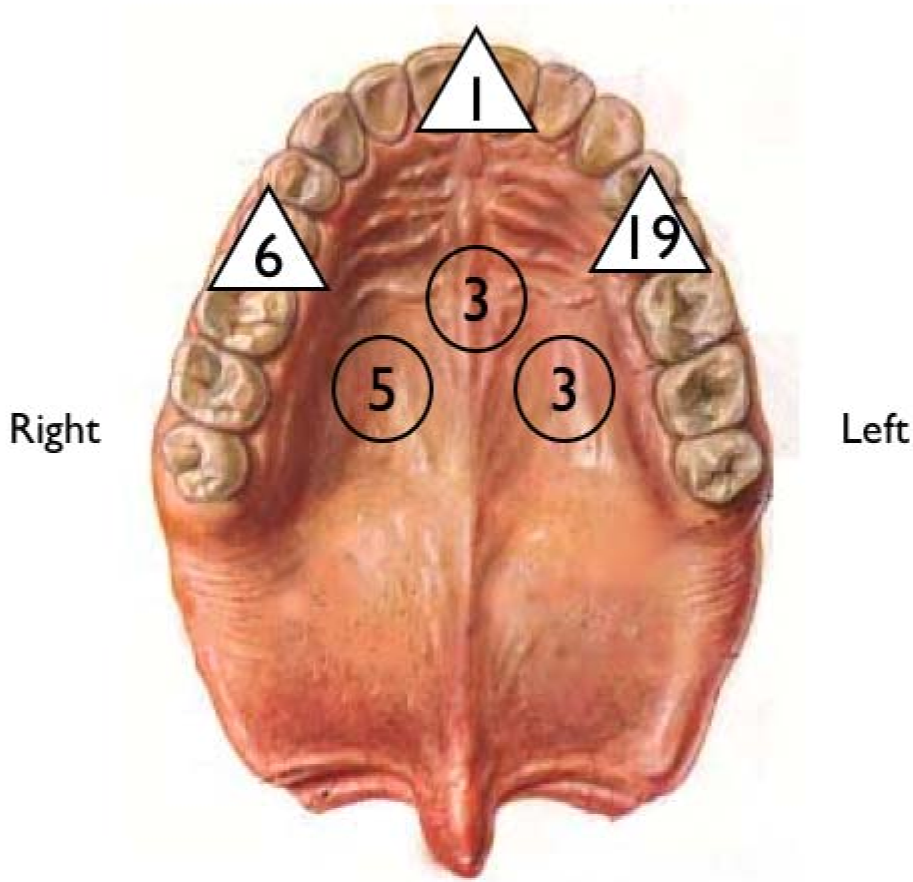

Figure 9. Diagram representing the location of tumors in the 37 patients with oral squamous cell carcinoma of the maxillary alveolus and hard palate.

Eight patients (21.6%) were treated with a solely palliative intent. Surgery was used as the primary treatment modality in 23 patients with 9 of these patients receiving postoperative radiotherapy. Radiation therapy was used as a single treatment modality in five patients (13.5%). One patient was treated with radiotherapy and chemotherapy (Table 5).

Table 5. Treatment by stage.

Stage at Diagnosis	Surgery	Radiotherapy	Combination
Stage I	5		
Stage II	7	1	1
Stage III		1	3
Stage IV	2	1	6*
Not Staged		2	

(Eight patients were treated with palliative intent. * One patient was treated with radiation therapy and chemotherapy.)

In the 23 patients treated with surgery a transoral excision was used in 11 cases. In eleven patients a cheek flap was deemed necessary for adequate exposure. An operative report was not identified in one patient. Margins on permanent section were found to be clear in 16 patients, close or within 2 mm in 3 of the patients, and involved in 4 patients. Radiation therapy, whether used as an adjunctive or as a primary treatment modality, was delivered by conventional fractionation at doses ranging from 4,125 to 7,000 CGy. Four of the seven patients presenting with positive lymph nodes were treated with a curative intent. Two of these patients were treated with radiation alone. In the remaining 25 node negative patients who were treated with curative intent, the neck was treated electively in 2.

Ten of the 29 patients treated with curative intent failed treatment with 6 failing at the primary site and 4 failing in the neck. The absolute and disease free survival at 5-years was 33% and 62% respectively (Figures 3 and 4). The 5-year disease-free survival (Figure 5) was 82% for stage I & II and 48% for stage III and IV ($p=0.056$). The initial treatment modality whether surgery, radiotherapy, or a combination of both significantly influenced the 5-year survival rate ($p=0.001$). No patient treated with radiotherapy as a single treatment modality survived 5 years or longer. The 5-year disease- free survival for patients treated with surgery alone, and a combination of surgery and radiotherapy was 69% and 73% respectively. Margin status did not affect survival in any of the cases with involved margins.

5.3 Maxillary Artery

Superficial (lateral) course of the maxillary artery to the lower head of the lateral pterygoid muscle

The lateral or superficial position of the second part of the maxillary artery in relation to the lower head of the lateral pterygoid muscle was found in 68% of all the specimens examined. In the male cadavers, the second part of the maxillary artery was found to be superficial in 71% of the total number of cases ($p= 0.052$). On the other hand, in the female cadavers, the artery was found to be superficial to the lower head of the lateral pterygoid muscle in 65% of the total number of cases ($p= 0.117$). There was no statistically significant variation in the course of the maxillary artery between both sides of the same cadaver and between the sexes (Figure 10).

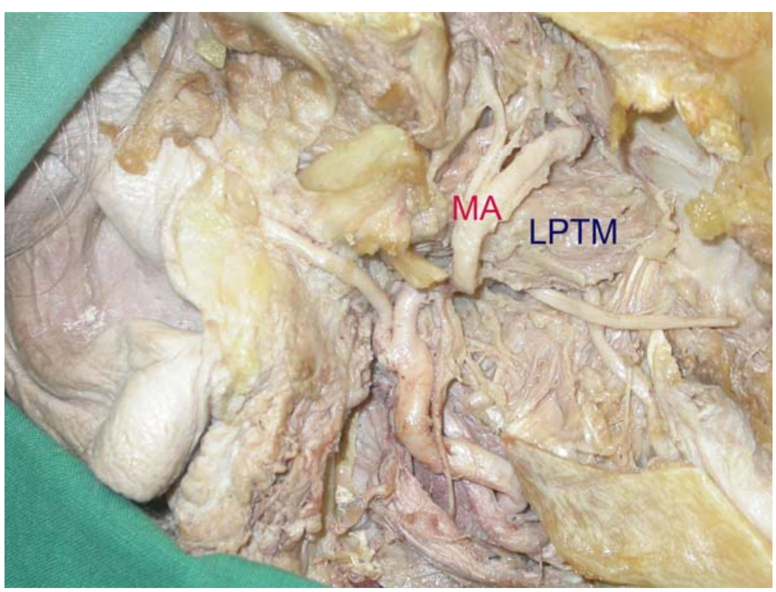

Figure 10. Superficial course of the maxillary artery over the lower head of the lateral pterygoid muscle. Lateral pterygoid muscle (LPTM). Maxillary artery (MA).

Deep (medial) course of the maxillary artery to the lower head of lateral pterygoid muscle

The frequency of the deep (medial) course of the second part of maxillary artery was relatively low. The maxillary artery was found to run deep to the lower head of the lateral pterygoid muscle in only 32% of all the cases. In the male cadavers, the incidence was 29%, while in the female cadavers it was 35% (Figure 11). While there was a trend for female cadavers to display the deep course of the maxillary artery more often than males, this difference was not statistically significant. Similarly, there was no statistically significant variation in the deep course of maxillary artery between the two sides in the same specimen and between both sexes.

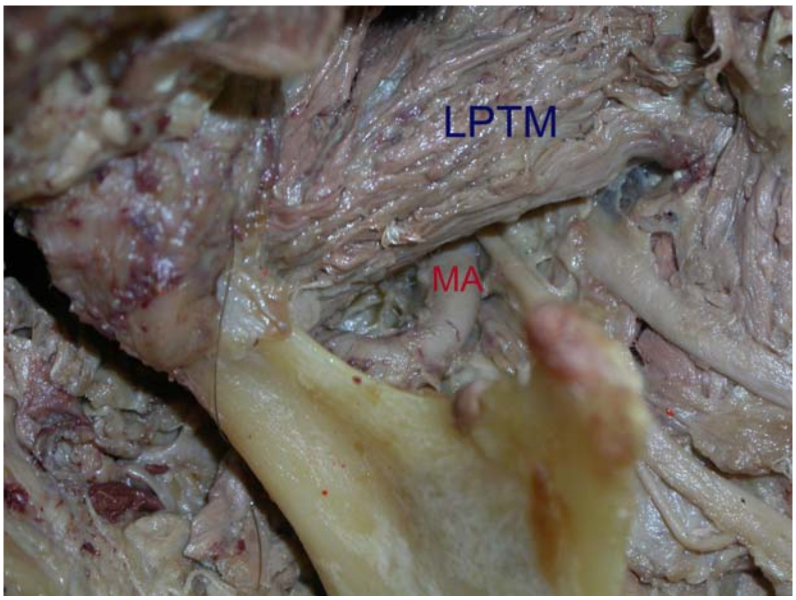

Figure 11. Deep course of the maxillary artery to the lower head of the lateral pterygoid muscle. Lateral pterygoid muscle (LPTM). Maxillary artery (MA).

5.4 Marginal Mandibular Nerve

The marginal mandibular nerve was managed with the intent to preserve function in 112 (84%) necks. The nerve was visualized in 76 (68%) of these patients. A decision to sacrifice the nerve, based on oncological considerations, was made in 21 dissections (Table 6).

Table 6. Management of the marginal mandibular nerve in 133 neck dissections. (Numbers in parenthesis are percentages)

Management Intent	Nerve Visualized	Nerve Not Visualized	Total
Preserve	76(68)	36(32)	112
Sacrifice	9(43)	12(57)	21
Total	85(64)	48(36)	133

Observations on the course and surgical relations of the marginal mandibular nerve were recorded in 85 patients. With the head in neutral position the nerve was at its lowest point 0.31±0.4cm (range 0.0-1.5 cm) below the inferior border of the mandible in the region of the posterior facial vein. (Figure 12) With the neck extended the nerve was displaced in an anterior and downward direction with the lowest point 1.25±0.7cm (range 0-3.0cm) below the mandible between the posterior and anterior facial veins ($p<0.01$). In the extended position the nerve was >1 cm below the lower border of the mandible in 42(54%) and >2 cm in 8(10%) of patients. (Table 7).

Table 7. Distance marginal mandibular nerve identified below the mandible with the neck in neutral and extended position in 78 neck dissections. (Numbers in parenthesis are percentages).

Distance Below Mandible	Neutral n=78	Extended n=78
>1 cm	3(4)	42(54)
>2 cm	0(0)	8(10)

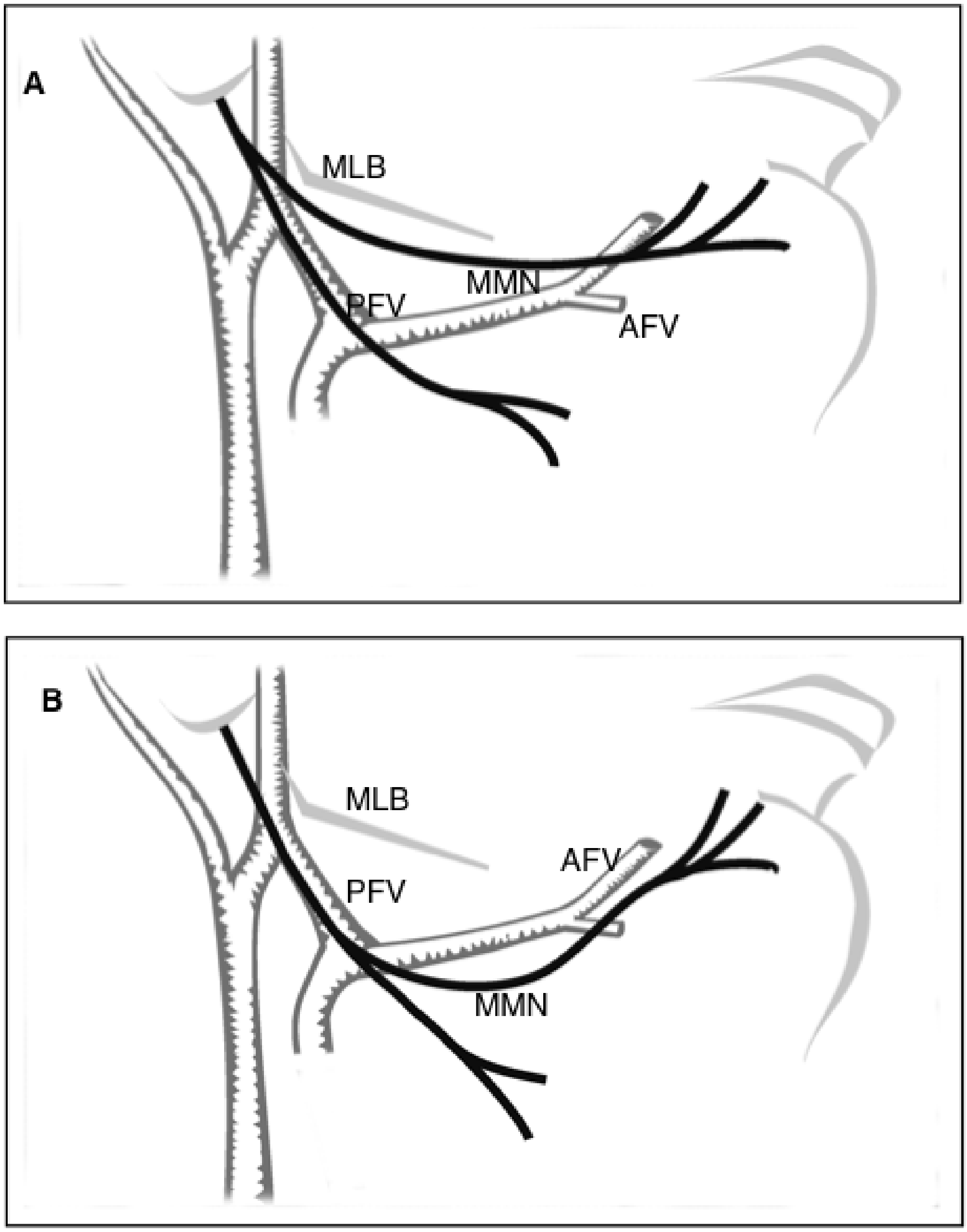

Figure 12. The relationship of the marginal mandibular nerve (MMN) to the lower border of the mandible (MLB), anterior facial vein (AFV) and posterior facial vein (PFV) with the neck in neutral position (A) and in extended position (B) with downward traction on the cervical fascia.

The functional status of the nerve was recorded following 121 neck dissections. Neuropraxia was recorded in 18(90%) of patients where the nerve was visualized and deliberately divided (n=9) or presumed divided with dissection in a plane superficial to platysma (n=11) for oncologic reasons. In the remaining 101 patients where the intent was to preserve the nerve praxia was observed in the immediate postoperative period in 29 and persisted in 16(16%). Temporary dysfunction of the marginal mandibular nerve had usually resolved by the second or third postoperative visits (3 to 6 months). Neuropraxia was not observed in the 24 patients where level I lymph nodes were not dissected. The incidence in the 77 patients where a level I dissection was performed with the intent to preserve nerve function was 16/77(21%). The relationship between nerve dysfunction and clinical and treatment related factors in this subset is shown in Table 8. The incidence of nerve dysfunction appeared to be higher when the neck dissection followed radiotherapy. This approached, but did not achieve statistical significance. Visualization of the nerve during neck dissection did not impact the functional outcome. The use of multivariate models did not establish any independent predictors of nerve dysfunction.

5.5 Resection Margin Status

The mean age of the cohort was 63.6±12.6 years with 58.89% males and 41.11% females. Tobacco or alcohol use or a combination of both was documented in 80% of patients. One hundred and ninety-eight - second primary malignancies were identified in 145 patients, of which 61% were metachranous. The tongue was the primary site in 129 (30.4%) of patients, floor of mouth in 169 (39.8%), lower alveolus in 38 (8.9%), buccal mucosa in 33 (7.8%), upper alveolus in 23(5.4%), and retromolar trigone in 33 (7.8%). One hundred and twenty-four patients had Stage I lesions, while 118, 68, and 105 patients had Stage II, III, and IV disease respectively. Ten patients could not be staged. One hundred and seven patients (26%) had clinically positive nodes at the time of presentation.

Table 8. Relationship of the status of the surgical margin to treatment parameters**.**

Variable	Involved (n=62)	Close (n=68)	Clear (n=295)
Resection			
Per-oral(n=243)	31(12.8%)	40(16.5%)	172(70.7%)
Composite(n=182)	31(17.1%)	28(15.3%)	123(67.6%)
Mandibulectomy			
Marginal(n=62)	8(12.9%)	14(22.6%)	40(64.5%)
Segmental(n=113)	23(20.3%)	15(13.3%)	75(66.4%)
None =(n=250)	31(12.4%)	39(15.6%)	180(72%)
Frozen Section			
Yes(n=225)	36(16.0%)	31(13.8%)	158(70.2%)
No(n=200)	26(13.0%)	37(18.5%)	137(68.5%)
Adjunctive Radiotherapy			
Surgery(n=298)	31(10.4%)	47(15.8%)	220(73.8%)
Surgery + Radiotherapy(n=127)	31(24.4%)	21(16.5%)	75(59.1%)

Surgery was used as a single treatment modality in 298 (70.1%) patients and 127(29.9%) received adjuvant radiotherapy (Table 8). Per-oral excision of the primary tumor was performed in 243 patients and 182 were managed with a composite resection. Mandible was resected in 175 patients, a marginal resection in 62 and segmental in 113. The clinically negative neck was treated electively in 120 patients (39.0%). Adjunctive radiotherapy was delivered by conventional fractionation, to a median dose of 5000 CGy (mode 5000 CGy). There were 4 deaths within 30 days of treatment completion. Minor morbidity was recorded in 23 patients treated with surgery (7.7%) and 42(33.1%) treated with adjunctive radiotherapy ($p<0.0001$). Major morbidity was observed in 8 (2.7%) of patients treated with surgery and in 10 (7.9%) of patients receiving radiotherapy ($P=0.0313$).

Sixty-two patients (14.6%) had microscopic tumor identified at the inked resection margin (Figure 8), 68 (16.0%) patients had close (<2mm), and 295 (69.4%) patients had clear (>2mm margins). The relationships between the status of the surgical margins and clinical data is shown in Table 8. Involved margins were observed less frequently following excision of tongue tumors, however the observed differences did not achieve statistical significance ($P=0.1239$). Involved margins were associated with both advanced T stage ($p=0.0033$) and the presence of clinically positive lymph nodes ($p=0.0034$). The type of surgical resection did not influence the incidence of involved margins (Table 8). The use of intra-operative frozen section was not associated with either involved or clear margins. Adjunctive radiotherapy was used more frequently in patients with involved margins ($p=0.0005$).

Table 9. Relationship of the status of the surgical margin to the incidence of recurrence, sites of initial recurrence, and 5-year overall survival (numbers in parenthesis are percentages).

	Involved(n=62)	Close(n=68)	Clear(n=295)	All(n=425)	P-Value
Recurrence	25(40.3)	26(38.2)	73(24.7)	124(29.2)	P=0.009
Site of Recurrence					
Primary Site	17(27.4)	16(23.5)	41(13.9)	74(17.4)	P=0.005
Neck	14(22.6)	11(16.2)	37(12.5)	62(14.6)	P=0.116
Distant Metastases	3(4.8)	5(7.4)	12(4.1)	20(4.7)	P=0.207
Overall Survival at 5 years	38.7%	58.3%	68.4%	61.9%	P<0.0001

Recurrent disease, observed most frequently at the primary site and neck, was observed in 78(43%) of patients treated with surgery and 46(36%) of patients treated with adjunctive radiotherapy (P=0.24). The relationships between margin status and the sites and incidence of recurrent disease and overall survival is shown in Table 9.

Table 10. Relationship of the status of the surgical margin to the incidence of recurrence, sites of initial recurrence, and 5-year overall survival (numbers in parenthesis are percentages).

	Involved(n=62)	Close(n=68)	Clear(n=295)	All(n=425)	P-Value
Recurrence	25(40.3)	26(38.2)	73(24.7)	124(29.2)	P=0.009
Site of Recurrence					
Primary Site	17(27.4)	16(23.5)	41(13.9)	74(17.4)	P=0.005
Neck	14(22.6)	11(16.2)	37(12.5)	62(14.6)	P=0.116
Distant Metastases	3(4.8)	5(7.4)	12(4.1)	20(4.7)	P=0.207
Overall Survival at 5 years	38.7%	58.3%	68.4%	61.9%	P<0.0001

Patients with involved and close margins had a similar incidence of treatment failure, which was significantly higher than that observed in patients with clear margins (Table 10). Failure at the primary site was more frequent in the presence of both involved and close margins. Margin status was not associated with failure in the neck or distant metastases. One hundred and ninety-eight deaths were documented, 73 attributed to oral cancer, 51 to second primaries, 44 from other conditions, and could not be accurately determined in 30. Sixty-two percent of the cohort survived 5 years. Overall survival was significantly worse for patients with involved margins when compared to those with close or clear margins (Figure 1).

The Cox's proportional hazard model is shown in Table 11. Age, T Stage, N Stage, and involved margins had a significant impact on 5-year survival. After controlling for the confounding variables the presence of tumor at the inked resection margin increased the risk of death by 90% (HR 1.9). The presence of a close margin did not have a significant impact on survival.

Table 11. Cox's proportional hazard model predicting 5-year overall survival.

Variable	**Hazard Ratio**	**95% CI**	**P-Value**
Included in the model			
Involved vs Clear/Close Margin	1.9	(1.2,2.9)	0.0026
Age ≥65 vs Age <65	1.5	(1.1,2.2)	0.0017
T Status	1.4	(1.2,1.6)	0.0002
N Status	1.3	(1.0, 1.6)	0.0465
Excluded from the model			
Close vs Clear Margin			0.1027
Gender			0.3212
Treatment Modality			0.6105
Stage			0.8805
Site			0.8379

6 Discussion

6.1 Retromolar Trigone Carcinoma

This series of 76 patients with RMT squamous cell carcinoma is comparable in many respects, including the age and sex distribution, etiologic factors, and incidence of second primaries, to most series of oral cancer. However, in contrast to other series this is a population-based study, describing events over a decade within a well-defined geographic boundary, the Province of Manitoba in Canada, with a population of 1.5 million.

The authors have developed the clinical impression that patients with early stage disease of the RMT fail treatment more frequently than observed with similar staged lesions of the tongue and floor of mouth. Survival of greater than 80% has been reported for early staged lesions of the tongue and floor of mouth (Lehman et al 1982, Shaha et al 1984, Franceschi et al 1993, Hicks et al 1997, Woolgar et al. 1999).

The previously reported prognosis for squamous cell carcinoma of the RMT is relatively poor with overall survival ranging from 26% to 80% (Byers et al 1984, Lo et al 1987, Kowalski et al 1993, Huang et al 2001, Genden et al 2003, Ayad et al 2005, Mendenhall et al 2005). Unlike the previous studies the overall survival of 51.4% in our series does not reflect a selection bias for patients and initial treatment modality such as radical surgery (Kowalski et al 1993) or treatment with radiation alone (Lo et al 1987, Huang et al 2001, Ayad et al 2005). The outcome reported in this study includes all patients managed specifically with squamous cell carcinoma of the RMT.

Clinical stage and survival did not show a significant correlation in this review. The lack of significance may be a function of the small sample number in each of the subdivided groups. While Kowalski’s team reported similar findings (Kowalski et al 1993); other investigators (Ayad et al 2005, Mendenhall et al 2005) have shown a significant influence on stage and survival with both univariate and multivariate analysis.

The initial treatment modality did not affect survival in this series, which is again consistent with previous reports (Byers et al 1984, Lo et al 1987, Kowalski et al 1993). Surgery seems to have the best survival rate, even if this is not statistically significant. The lack of success may have been due to the small sample number in each treated group. More recent reports of treatment outcomes for squamous cell carcinoma of the RMT suggest that survival is improved with surgery followed by adjunctive radiation therapy (Huang et al 2001, Antoniadoes et al 2003, Mendenhall et al 2005).

The surgical margin status impacted local-regional treatment failure as reflected by a significant decrease in overall survival with positive margins. This was the only significant predictor of outcome in this series. This is consistent with some previous reports involving other sites and types of oral cancer (Looser et al 1978, Batsakis JG 1999). However the margin status was not found to predict survival in some other series (Kowalski et al 1993, Huang et al 2001). This outcome was attributed to the use of postoperative radiotherapy by one investigator (Huang et al 2001).

The lack of concordance between studies with respect to prognostic factors for squamous cell carcinoma of the RMT again reflects small sample sizes with differences in patient selection. Larger multicenter population based studies using appropriate multivariate models are necessary to resolve these issues.

There has been no agreement on the optimal management of these tumors of the RMT. Early reports recommended surgical treatment over radiotherapy (Barbosa 1959) with reports of experiences with extended commando operations in 114 patients with or without postoperative radiation resulting in a 5-year absolute survival rate of 55.3% (Kowalski et al1993). The conclusion in this series was that adjunctive radiotherapy improved local and regional control (Kowalski et al 1993). The MD Anderson experience showed a recurrence rate of 16% in patients treated with radiation therapy alone and 18% in patients treated with post operative radiation (Byers et al 1984). The 5 year absolute survival was 26%. In another report from the same institution the experience with irradiation of carcinoma of the anterior faucial pillar and the RMT showed the 5-year determinant survival to be 83% (Lo et al 1987). A more recent study reported a 5-year actuarial survival of 60.6% in 50 patients treated with surgery with 24 receiving adjuvant therapy (Hao et al 2006).

Another review of 65 patients showed a 5-year disease free survival of 31% with radiation alone, compared to 90% and 63% with surgery and pre- or postoperative radiation respectively (Huang et al 2001). These authors recommended combined surgery and radiotherapy for all stages of disease. The most recent review in 2005 reported 5-year overall survivals of 40% and 56% in 35 patients managed with radiation alone and 64 managed with surgery and radiotherapy respectively (Mendenhall et al 2005). Using a multivariate analysis this study found the stage ($p=0.0476$) and the treatment modality ($p=0.0098$) to be significant predictors of survival (Mendenhall et al 2005). One other study has shown improved survival with the addition of chemotherapy to surgery and radiation (Lo et al 1987).

The optimal management of squamous cell carcinoma of the RMT cannot be determined from this or any other review. When considering relatively uncommon tumors such as squamous cell carcinoma of the RMT there is a need for the head and neck oncology community to pool population based outcome data to establish accurate prognostic indicators.

6.2 Carcinoma of the hard palate and maxillary alveolus

Squamous cell carcinoma of the maxillary alveolus and hard palate is relatively uncommon in western society (Bhansali 1961, Ong 1970, Kroll & Hoffman 1976). It has been noted that neoplasias, both SCC and non SCC, of the upper jaw constitute only 2% of all head and neck malignancies, and 10% of oral cancers (Petruzzelli & Meyers 1994). These lesions appear to be considerably more common in India accounting for 40 to 55% of the oropharyngeal cancers (Ramulu & Reddy 1972, Reddy 1974). The relatively low numbers of these tumors is the most likely reason these lesions are often grouped and reported together with other sites such as the mandibular alveolus (Cady & Catlin 1969, Soo et al 1988, Gomez et al 2000) and soft palate (Cady & Catlin 1969, Evan & Shah J 1981, Shibuya et al 1984) or combined with salivary gland tumors (Evan & Shah 1981). In contrast to most other reports this study examines treatment outcomes in a site which is anatomically specific and is pathologically limited to squamous cell carcinoma of the maxillary alveolus and hard palate in a population based historical cohort.

The anatomical characteristics of the maxillary alveolar ridge and hard palate are similar as together they form the roof of the oral cavity and the floor of the nasal cavity and maxillary sinus. Full thickness resection of the structures involved by tumor at this site will result in oro-nasal and oral antral communication, a problem unique to this site. This unique anatomic relationship makes the radiographic work-up with CT scans and MRI scans crucial to determine tumor extent and stage. This radiographic visualization ultimately helps decides the staging, the extent of surgical resection and the use of other modalities of treatment.

Therefore, the clinical presentation, the surgical management and reconstructive considerations including the management of oro-nasal and oral antral communication with immediate obturation, are similar for these sites (Figures 1a to 1d). From a clinical perspective it is often difficult in advanced tumors to determine the exact epicenter (Figure 2). The maxillary alveolus and hard palate, in contrast to the remainder of the oral cavity, seems to share a female predilection in this and other reports (Chung et al 1979, Chung et al 1980, Yoruzu et al 2001). In searching the literature further, the authors were unable to find reasons for this female predilection as of yet. However, based on the foregoing, the authors feel that it is most appropriate to consider SCC of the upper alveolus and hard palate as a single entity.

The overall or absolute survival of 33% at 5 years reported in this study is relatively low. Reported survival rates for these sites which range from 21 to 76% (Cady & Catlin 1969, Evan & Shah 1981) are difficult to interpret as they are often grouped to include other sites and other pathological entities such as salivary gland tumors. The Improved disease free survival at 5 years of 62% reported in the current study reflects the influence of advanced age of the patients with significant co-morbidities on overall survival. These considerations as well as the frequency of stage IV disease (40%), account for the relatively large number of patients not amenable to treatment with curative intent.

Margin status did not affect survival or outcome in any of the cases with involved margins. The reality is that this is a study of only 37 cases in a rare site and the author's did not feel comfortable drawing conclusions from such a small sample.

The number of participants in this study is too small to examine prognostic factors in detail. In this report there was a trend towards decreased survival with advanced stage of disease as observed in other series (Chung et al 1979, Yoruzu et al 2001). Yokoo et al (2002) were unable to correlate stage of disease with prognosis. In their series 80% of patients had stage IV tumors. They proposed a new classification system dependent upon the involvement of the maxillary sinus or nasal floor. The authors of the present study observed improved survival in patients treated with surgery. Arguments in favor of one treatment modality over another in this, and the other series reviewed, are of limited value because of small sample size in the studies.

There seems to be better prognosis for Stage III and IV lesions at this site compared to the late stages at other oropharyngeal sites. This trend was confirmed in other series (Chung et al 1979, Yoruzu et al 2001, Yokoo et al 2002). The reasons for this are unknown and not apparent in the literature. The authors feel that this may be due to differences in lymphatic drainage at the maxillary alveolar and palatal sites when compared to other oropharyngeal sites. This tumor is more prevalent in India and these numbers may also represent some geographic differences potentially due to differences in social habits such as reverse cigarette smoking. The authors feel that the numbers in the current study are too small to be able to make further conclusions at this time.

In conclusion squamous cell carcinoma of the maxillary alveolar ridge and hard palate differs from other oral cancers in several aspects. SCC tends to occur at these sites in a relatively older population with a female predilection. A relatively high number of patients were not amenable to treatment with curative intent. Surgical treatment with or without radiation therapy, appears to improve disease control. A future prospective multi-center study with a larger cohort of patients may help to answer questions regarding the prognosis of treatment related to the specific stages of this disease.

6.3 Maxillary Artery

Understanding the course of maxillary artery in the infratemporal fossa with its variation is of potential of interest to many practitioners who treat patients with lesions of the cranio-maxillofacial region. For instance, tumors arising or extending into the infratemporal fossa via foramen ovale or foramen rotundum, such as juvenile nasopharyngeal angiofibromas, are commonly excised by lateral cranial base approaches such as the Fisch type C (Allen et al 1974, Fisch & Pilsbury 1997) or subtemporal / infratemporal approaches (Fisch 1978, Fisch 1982, Gates 1988, Holliday 1986, Mickey et al 1988). In these approaches, the entire contents of the infratemporal fossa are exposed including the maxillary artery, which may be greatly susceptible to damage or sacrifice, depending on the extent of the surgery and the size of the tumor. Therefore, knowing the course of the maxillary artery and its variations will aid in surgical planning and in minimizing intraoperative or postoperative hemorrhage.

In orthognathic and temporomandibular joint surgery, many surgical procedures are performed in close proximity to the maxillary artery in the infratemporal fossa. Mandibular osteotomies, such as intra-oral vertical ramus osteotomy (IVRO) or bilateral sagittal split osteotomy (BSSO), are commonly performed to correct dentofacial deformities (Fujimura et al 2006). Open temporomandibular joint procedures using the preauricular approach are relatively commonly used. These surgical procedures or approaches have been developed to improve safety in order to minimize or prevent damage to vital anatomic structures such as the maxillary artery. Avoidance of the maxillary artery or to one of its branches is necessary to prevent extensive hemorrhage intraoperatively or postoperatively (Apinhsmit et al 2004, Fujimura et al 2006).

In clinical dentistry, mandibular blocks (Coleman & Smith 1982) such as Gow-Gates or Akinosi, are very commonly used techniques to deliver local anesthetic agents prior to many dental procedures. The site of injection is extremely close to the branches of the maxillary artery, which may result in undesirable consequences, such as intrarterial injection or hematoma (Frangiskos et al 2003). The clinician must be fully aware of the course of the maxillary artery and its variations in order to prevent the side effects from intra-arterial local anesthetic injection.

The course of the maxillary artery in relation to the inferior head of the lateral pterygoid muscle has been a controversial point. As a result, a number of studies were conducted to investigate this mutual relationship. A review of the literature showed that many authors found the maxillary artery superficial to the lower head of lateral pterygoid muscle. This finding ranged between 54% and 70% (Thompson 1891, Lurje 1946, Laskar et al 1951, Skopakoff 1968, Vironis 1996, Orbay 2006). Moreover, Adachi (1928) found a higher frequency of superficiality (93%) in the Japanese population, raising the possibility of racial differences. However, Lauber (1901) in his investigation showed only 8.5% of the Caucasian population with a superficial maxillary artery. In the present study, the relationship of maxillary artery to the lower head of the lateral pterygoid muscle was generally similar to that of other studies. On the one hand a trend was noted in the lateral course of the maxillary artery relative to the lower head of the lateral pterygoid muscle to be more common in males (71%) than in females (35%), supporting other data in the literature (Thompson 1891, Lurje 1946, Laskar 1951, Skopakoff 1968, Vrionis et al 1996, Orbay et al 2006). On the other hand, the medial course was less common in males (29%) than in females (35%) in the present study. However, the course of the maxillary artery in relation to the lower head of the lateral pterygoid was symmetrical in all of our specimens. This is not in agreement with the report by Pretterklieber and co-workers, which is the only study that shows asymmetry to exist in the course of the maxillary artery between the two sides in the same specimen (Pretterklieber et al 1991). This finding is questioned because there is no other supporting work in the literature.

Many authors attempted to explain the potential factors that determine the position of maxillary artery relative to the lateral pterygoid muscle in the infratemporal fossa. However, craniometric analysis, including facial height, cranial breadth or length, and cephalic index, did not reveal any correlation between the variable position of the maxillary artery and the measured craniometric parameters (Skopakoff 1968, Macho 1986, Sjovold 1988, Vertcauteeren 1990, Pretterklieber et al 1991, Vrionis et al 1996, Orbay et al 2006). In another study the lateral course of the maxillary artery was found to be more common in brachycephalic and mesocephalic individuals (Lurje 1946). However, this study by lacked any statistical evaluation and was contradicted by other studies (Laskar et al 1951). One theory, the metabolic hypothesis (Adair et al 1990) was proposed to explain the potential factors involved in angiogenesis and the vascularization of growing tissues, however, it failed to explain the factors responsible for variation in the position of the second part of the maxillary artery relative to the lateral pterygoid muscle.

In conclusion, this study confirms some of the earlier findings concerning the more common superficial position of the maxillary artery in relation to the lateral pterygoid muscle. However, the findings that there was a trend for the deeper course of the second part of the maxillary artery to be slightly more common in females than in males, and that there was no evidence of asymmetry in the course of the artery within the two sides of the same specimen, were unique to this study. The mechanism responsible for determining the relative position of the artery to the lateral pterygoid muscle is still unknown. This study helps to begin to define the question of the effect of ethnicity on the relative position of the maxillary artery to the inferior head of the lateral pterygoid muscle by studying a Caucasian population from Canada. Comparison with future studies in other ethnic groups (Apinhsmit et al 2004) will further help to answer this question.

The relationship between the maxillary artery and the lateral pterygoid muscle may be important during major facial reconstruction, cleft craniofacial reconstruction, cancer surgery, and surgery to the temporomandibular joint. The anatomy of the terminal end of the maxillary artery should be kept in mind during surgical dissection.

6.4 Marginal Mandibular Nerve

The complication of marginal mandibular nerve injury following neck dissections for malignant disease has not received much attention when compared to other complications of head and neck surgery (Moffat & Ramsden 1977). This is not surprising as historically other morbidities of major head and neck resections have over shadowed this disability as they were much more overwhelming. The significance of asymmetry of the lower lip increases as morbidity from other aspects of the treatment is minimized through multimodal treatment plans that incorporate conservative surgical approaches and organ preservation protocols. The frequency of nerve dysfunction observed in this prospective evaluation of neck dissections, is comparable to that reported in retrospective reviews of outcome following excision of the submandibular gland for benign disease (Hald & Andreassen UK 1994). It is recognized that retrospective studies underestimate the true incidence of complications (Hald & Andreassen 1994, Tulley et al 2000).

This series represents a heterogeneous population of patients with respect to pathology, clinical, and treatment related parameters including the extent of neck dissection. In the cases where praxia of the marginal mandibular nerve was observed following a neck dissection with visualized or presumed division of the nerve, the outcome of the nerve could usually be predicted preoperatively. These patients generally had advanced local or regional disease. Patients where level I nodes were not dissected were included in the functional assessment as the proximal marginal mandibular nerve is exposed to potential traction type injury from retraction to expose high jugulodigastric lymph nodes. The absence of nerve dysfunction in this cohort of patients may be explained by the fact that the nerve is well protected by surrounding soft tissue. When level I was dissected and the intent was to preserve the nerve the incidence of praxia appeared to be higher after preoperative radiotherapy. The majority of patients in this series were managed surgically within 6 to 8 weeks of completion of radiotherapy. Tissue planes tended to be edematous, however the anatomy was not distorted. The fact that no independent predictors of nerve dysfunction were identified in patients where level I was dissected suggests that anatomic considerations are paramount in preserving the function of the marginal mandibular nerve.

The anatomy of the marginal mandibular nerve in its vulnerable position in the upper neck is variable between patients. The course and position of the nerve also varies with the position of the head and downward traction on the investing layer of cervical fascia. The dynamic nature of the nerve was evident in this study. This explains, in part, the discrepancies between cadaver studies and clinical observations. Cadaver tissue is contracted and relatively immobile. Of interest when fresh, as opposed to embalmed cadaver material is studied, the nerve is consistently reported below the lower border of the mandible. In a series of 22 fresh cadavers found the nerve below the mandible in 63% of specimens posterior to the facial artery and in 27% anterior to the artery (Savary et al 1997). Savary et a (1997) observed some branches as low as 3-4 cm below the lower border of the mandible. The marginal mandibular nerve was well below the inferior border of the mandible in almost every instance in fresh cadaver specimens and clinical dissections (Nelson & Gingrass 1979). These authors therefore recommended cervical incisions several centimeters below the inferior border of the mandible (Nelson & Gingrass 1979). The present study confirms the consistent course of the marginal nerve below the inferior border of the mandible. The observation that the nerve is drawn downward when the neck is extended (Baker & Conley 1979) has been confirmed by the present study. The placement of cervical incisions 2 cm below the lower border of mandible will place the nerve at risk in a significant number of patients (Baker & Conley 1979).

Detailed anatomic dissections (Dingman & Grabb 1962, Nelson & Gingrass 1979, Skandalakis et al 1979) show that there are often multiple contributions to the marginal mandibular nerve and that it can be difficult to discern between mandibular and platysmal branches. Dingman and Grabb noted that in many specimens fine branches could be seen running along the lower border of the mandible, some up to 2 cm below it (Dingman & Grabb 1962). They stated that these branches terminated in and innervated the platysma in all specimens. Nelson and Gingrass argued that these same branches, when followed anteriorly in fresh cadaver specimens and in clinical practice, ascended over the lower border of the mandible to innervate specific lip depressors. They contend that these branches should be identified as mandibular and not cervical branches (Nelson & Gingrass 1979). Skandalakis and co-workers described an anterior ramus of the cervical division of the facial nerve that joins the mandibular ramus to contribute to the innervation of the lower lip (Skandalakis et al 1979). There are also observations that the platysma, innervated by the cervical division of the facial nerve, contributes to depression of the lower lip (Tulley et al 2000). Division of the cervical branch of the facial nerve or the platysma can result in a pseudo-paralysis of the marginal mandibular nerve that usually recovers spontaneously (Ziarah & Atkinson 1981). Detailed dissections of the marginal mandibular nerve were not done in our study. From a practical point of view there is usually a single identifiable nerve rami coursing superficial to the facial veins which results in asymmetry of the lower lip if divided. Stern indicates that if the structure in question during dissection does not course above the inferior border of the mandible within 2 cm of the facial vessels then that structure is not the marginal mandibular nerve (Stern 1992).

A low cervical incision with a "nonvisualization" approach the marginal mandibular nerve is supported (Ichimura et al 1979, Smith et al 1993) for management of benign disease of the submandibular gland. In this study visualization of the nerve during the course of a neck dissection was not associated with a lower incidence of nerve dysfunction. The following technical considerations should minimize injury to the marginal mandibular nerve in the context of a neck dissection. Irrespective of the site of the skin incision skin flaps should be carefully elevated in a plane immediately deep to platysma and superficial to the investing layer of deep cervical fascia and marginal mandibular nerve. It is not the level of the skin incision that is important but the level of transection of investing layer of cervical fascia. Knowledge of the dynamic and variable location of the marginal mandibular nerve relative to the inferior border of the mandible is useful in this regard. The decision to visualize the nerve needs to be individualized (Stern 1992). If it is deemed necessary to divide the cervical fascia within 3-4 cm of the inferior border of the mandible it is our opinion that an attempt should be made to visualize the course of the nerve. The nerve is then preserved or sacrificed based on the oncologic objectives of the procedure. In our opinion electrical cautery should be used sparingly and attention should be directed to avoiding traction or pressure injury from retractors.

6.5 Resection Margin Status

This historical cohort study of patients with squamous cell carcinoma of the oral cavity is relatively large. It is comparable in most respects, including the age and sex distribution, site distribution, etiologic factors, and incidence of second primaries, to most series of oral cancer**.** The incidence of involved margins (microscopic tumor at the inked resection margin) observed in this population based historical cohort was 14.6%. The reported incidence of involved margins following resection of head and neck cancers varies widely from 1 to 22% (Looser et al 1978, Chen et al 1987, Loree & Strong 1990, Jacobs et al 1993, Jones 1994, Spiro et al 1999, Sessions et al 2002, Sutton et al 2003, Kademani et al 2005). These studies with one exception (Jacobs et al 1993) report single institutional experience and often include extra- oral sites (Looser et al 1978, Chen et al 1987, Loree & Strong 1990, Jacobs et al 1993, Jones 1994). Margins are more often positive in oral cancer than other sites in the head and neck (Jones 1994, Woolgar & Triantafyllou 2005).

Tumor at the inked resection margin increased recurrence rates in this study consistent with previous observations (Looser et al 1978, Loree & Strong 1990, Jacobs et al 1993, Spiro et al 1999, Sutton et al 2003). An independent and significant impact on overall survival was demonstrated. Involved margins were associated with an increased tumor load, advanced T and N status, on presentation. The association of involved margins with factors that can independently influence outcome in oral cancer such as stage of disease (Ravasz et al 1991, Sutton et al 2003, Ravasz et al 2005) and adverse histopathological features such as tumor thickness (Yuen et al 2000) and unfavourable patterns of invasion (Woolgar et al 1995, Sutton et al 2003, Kademani et al 2005) make the use of multivariate models necessary to assess the complex interactions of margin status and survival. Sutton et al (2003), in a detailed analysis of the impact of margin status on outcome, included clinical findings as well as histopathology data including nodal involvement and extracapsular spread, pattern of invasion, perineural invasion and vascular permeation in their multivariate model. The relative risk of death for involved margins was 11.61(P=0.0013) and close margins 2.66(p=0.02). The only other factor with a significant impact on survival was positive lymph nodes (HR 2.15, p=0.063). Other studies have failed to show an independent effect of positive or inadequate margins on survival with multivariate analysis (Jones 1994, McMahon et al 2003, Kademani et al 2005). Theses studies are not strictly comparable to the above series as they included significant numbers of patients with extra-oral tumors (Jones 1994, McMahon et al 2003) previously treated patients (Jones 1994) and a different definition for the "positive margin" (McMahon et al 2003, Kademani et al 2005).

Close margins (<2mm) had a similar impact on the incidence and pattern of local recurrence as involved margins. Survival was not adversely effected by the close margin. Many investigators consider both close, and tumor at the inked resection margins together in their analysis of the impact of margin status on outcome (Sadeghi et al 1986, Ravasz et al 1991, Woolgar et al 1995, van Es et al 1996, Slootweg 2002). When the impact of the close margin is reported separately the results suggest that the prognosis is better than observed in patients with tumor at the resection margin (Chen et al 1987, Loree & Strong 1990 Sutton et al 2003, Chandu et al 2005). A major problem in assessing and comparing the results of studies evaluating margins is the fact that some series include patients with close margins and others do not. This problem is further compounded by the lack of a standard definition for the close margin. The most widely accepted definition of a close margin is tumor within 5 mm of the inked resection margin (Looser et al 1978, Chen et al 1987, Loree & Strong 1990, Ravasz et al. 1991, Sutton et al 2003, Meier et al 2005). This is an arbitrary designation (Loree & Strong 1990, Batsakis JG 1999). Others use <2mm (Yuen et al 1998, Kademani et al 2005), <3mm (Chandu et al 2005), within one high power field (Spiro et al 1999) or a variable definition related to the pattern of invasion at the tumor host interface (Slootweg et al 2002). *In-situ* change and dysplasia have also been included ((Looser et al 1978, Sadeghi et al 1986, Chen et al 1987, Loree & Strong 1990, Ravasz et al 1991, Sutton et al 2003). This study did not address the impact of premalignant change at the margin. The balance of opinion would favor not including dysplasia in the definition (Meier et al 2005). The results of this study suggest that the outcome with tumor close to the resection margin should be reported separately from that observed with tumor at the inked resection margin as the prognosis differs. A standard definition for a close margin is necessary and this should be determined by a systematic evaluation of the effect of the width of resection on outcome.

Considering the significant impact on outcome precise definitions for the inadequate surgical margin are important clinically. Patients with assumed inadequate margins are considered for adjunctive radiotherapy. It is accepted that adjunctive radiotherapy in the setting of an inadequate may improve local-regional control (Meier et al. 1984, Zelefsky et al 1992, Zelefsky et al 2004) and possibly impact survival (Sessions et al 1986, Sessions et al 2002). Adjunctive radiotherapy did not impact local and regional recurrence or survival in this study. It did however significantly increase morbidity.

The surgical margin is a prognostic determinant that is, at least in part, under the control of the surgeon as he or she determines the extent of resection in the individual patient. The clinical margin necessary to achieve an adequate histological margin has to take into consideration the fact that surgical specimens shrink, in the order of 40-50% (Batsakis 1999) when fixed in formalin. Mucosal margins tend to receive the most attention, however most recurrences involve the deep resection margin. The importance of a 3-dimensional resection has been emphasized in the work of Ravaszc and co-workers (Ravasz et al 1991). Recurrence was not identified in patients with positive mucosal margins. Positive deep and multiple positive margins were associated with recurrence rates of 38% and 70% respectively (Ravasz et al 1991). The positive association of margin status with various tumor related factors observed in this and other studies indicates that negative margins are harder to achieve with large tumor loads, proximity to mandible and a posterior location in the oral cavity. The positive association of margins with unfavorable histopathology such as tumor invading deeply as nests and cords as opposed to a pushing front has prompted several investigators (McMahon et al 2003, Sutton et al 2003) to consider positive margins as an indicator of more aggressive disease. Patients with poor histopathological parameters with clear margins have a better outcome than patients with bad histology and positive margins (Ravasz et al 1991, van Es et al 1996). The patient's expectations for a functional outcome also influence the extent of resection. There is no single definition for an adequate clinical resection margin. As defined by Yuen and co-workers (Yuen et al 1998) the optimal resection margin should not compromise local control from an inadequate resection or cause unnecessary functional morbidity from too much resection. The use of intra-operative frozen section did not influence margin status in this study. Frozen section tends to emphasize mucosal and not the deep resection margin. In addition the common practice of assessing the patients resection margins (Yuen et al 2005), does not identify the patient with a close margin.

In summary the status of the surgical resection is an important predictor of outcome, both local recurrence and overall survival in oral cancer. The presence of tumor at the resection margin, and close to the resection margin should be considered separately with respect to prognostic significance. Intra-operative assessment of resection margins needs to emphasize involvement and proximity of tumor to the deep resection margin. There is a need for a standard definition for the close margin in oral cancer based on a systematic evaluation of the impact of the width of the margin on outcome.

6.6 Future Perspectives

Improvements in cancer management will help increase survival. Screening has been shown to help reduce mortality in breast and colorectal cancer (Hakama et al 2008). Efficacy in mortality end-point reduction from screening has also been reported for hepatocellular carcinoma and oral cancer (Hakama et al 2008). Such screening efforts are even more important as some types of oropharyngeal carcinomas have been reported to be increasing (Hammarstedt et al 2007). Knowing that oral cancer detection at earlier stages is linked to improved survival adds more support to the importance of effective screening programs (Sargeran et al 2008).

The link to potential causative agents must also continue to receive attention. The finding that there is consistency in exposure intensity across diverse caner sites suggests a general phenomenon and may provide clues to the molecular basis of smoking-related cancer risk (Lubin et al 2008). Exposure to chemicals and alcohol also adds to the risk of oral cancer (Tarvainen et al 2008). The role of HPV as a risk factor for tonsillar cancer may also provide clues for etiology and guide prevention programs involving risk reduction and possible vaccination (Hammarstedt et al 2006).

Surgical treatment may also become more sophisticated. Resection margin analysis and monitoring may lead to better guidance of the surgeon by histopathologic results (Naison et al 2009). Immunostaining of markers such as claudin 7 could be used for prognostic purposes in patients with SCC of the tongue (Bello et al 2008). While such advances may be for sites other than the RMT or the maxillary alveolus and hard palate, they represent potential advances in the management of oral SCC, a disease with uncertain prognostic outcomes to the present day.

7 Summary and conclusions

The following main conclusions can be drawn from the results obtained in the present studies:

1. The treatment outcomes of squamous cell carcinoma of the retromolar trigone using a population-based study resulted in an overall survival of 51.4% in this series. The optimal management of SCC of the RMT cannot be determined from this or any other single review. When considering relatively uncommon tumors such as SSC of the RMT there is a need for the head and neck oncology community to pool population based outcome data to establish accurate prognostic indicators.

2. Squamous cell carcinoma of the maxillary alveolar ridge and hard palate differs from other oral cancers in several aspects. SCC tends to occur at these sites in a relatively older population with a female predilection. The treatment outcomes of SSC of the maxillary alveolus and palate using a population-based study showed that a relatively high number of patients were not amenable to treatment with curative intent. Treatment with surgery, with or without radiotherapy, appeared to improve disease control. A future prospective multi-centre study with a larger cohort of patients may help to answer questions regarding the prognosis of treatment related to the specific stages of this disease.

3. The relationship of the maxillary artery and the lateral pterygoid muscle in ethnic samples is important in oral cancer care due to potential ethnic variations. These variations should be considered in planning of surgery in this anatomic region.

4. The anatomy and function of the marginal mandibular branch of the facial nerve pertains to the surgical management of oral cancer as the function of this nerve may need to be sacrificed, causing significant facial disfigurement. Resections should be approached on a case-by-case basis as should the perceived need for the complete dissection and identification of the MMN. The goal should be to minimize disfigurement due to nerve palsy where possible.

5. The significance of the positive surgical margin in oral cancer management was assessed. The status of the surgical resection is an important predictor of outcome, both local recurrence and overall survival in oral cancer. Intra-operative assessment of resection margins needs to emphasize involvement and proximity of tumor to the deep resection margin.

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9 Role in publications

List of papers:

I. **Binahmed A**, Nason RW, Abdoh AA, Sándor GKB (2007). *Population-based study of treatment outcomes in squamous cell carcinoma of the retromolar trigone.* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 104: 662-665. Epub 2007 Aug 29.
Role: Collected and analyzed data, statistical analysis of results with the help of Dr. Abdoh, wrote paper.

II. **Binahmed A**, Nason RW, Hussain A, Abdoh AA, Sándor GKB (2008). *Treatment outcomes in squamous cell carcinoma of the maxillary alveolus and palate: A population-based study*. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 105: 750-754. Epub 2008 Feb 23.
Role: Collected and analyzed data, statistical analysis of results with the help of Dr. Abdoh, wrote paper.

III. Hussain A, **Binahmed A**, Karim A, Sándor GKB (2008)**.** *Relationship of the maxillary artery and lateral pterygoid muscle in a caucasian sample.* Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology. 105: 31-35. Epub 2007 Aug 29.
Role: Performed dissections, collected data, statistical analysis and wrote paper.

IV. Nason RW, **Binahmed A**, Torchia MG, Thliversis J (2007). *Clinical observations of the anatomy and function of the marginal mandibular nerve*. Int J Oral Maxillofac Surg. 36: 712-715. Epub 2007 March 27.
Role: Performed dissections, collected data, statistical analysis and wrote paper

V. **Binahmed A**, Nason RW, Abdoh AA (2007). *The clinical significance of the positive surgical margin in oral cancer*. Oral Oncol. 43: 780-784.
Role: Collected and analyzed data, statistical analysis of results with the help of Dr. Abdoh, wrote paper.

Original Publications

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Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

ORAL AND MAXILLOFACIAL PATHOLOGY *Editor: Mark W. Lingen*

Population-based study of treatment outcomes in squamous cell carcinoma of the retromolar trigone

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Background. Carcinoma of the retromolar trigone is relatively uncommon. High rates of local recurrence account for a relatively poor prognosis.
Study design. A population-based historical cohort of 76 cases with biopsy-proven squamous cell carcinoma of the retromolar trigone were studied as a case series. Kaplan-Meier survival curves and log rank test were used for statistical analysis.
Results. The mean age was 67.2 years. Fifty-six patients were male, 45% had T1 or T2 tumors, and 61% were staged as N0. Treatment included radiotherapy in 35%, surgery alone in 26%, surgery and radiotherapy in 23%, and 16% received palliative treatment. The absolute and disease-specific survivals at 5 years were 51.4% and 67.7%, respectively. In patients treated with surgery, the resection margin status predicted the overall 5-year survival (P = .027), with 75% of patients with negative margins surviving 5 years versus a survival of 0% of patients with involved margins.
Conclusions. Squamous cell carcinoma of the retromolar trigone has a poor survival rate for early-stage disease. Adequate surgical margins can improve survival. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:662-5)**

The retromolar trigone (RMT) is an ill-defined triangular area in the oral cavity posterior to the upper and lower third molar teeth, with the maxillary tuberosity at its apex. The RMT is continuous laterally with the buccal mucosa and medially with the soft palate. Superiorly and inferiorly the RMT blends with the mucoperiosteum of the maxillary and mandibular alveoli.[1] The RMT is a relatively uncommon site for oral squamous cell carcinoma. The etiology of these tumors, as for other sites of oral squamous cell carcinoma, has been linked to tobacco and alcohol use.[2,3] Tumors of the RMT are often confused with tumors of the tonsil, soft palate, or alveolar ridge. Tumors in this region are characterized by early invasion of the mandible and the adjacent buccal mucosa and soft palate (Fig. 1).[3,4] They are often diagnosed at an advanced stage owing the absence of early symptoms. The prognosis tends to be poor because of the advanced stage of disease at the time of presentation.[2,3,4] In their advanced stage, pain and trismus are common from the invasion of the buccal, lingual, and inferior alveolar branches of the mandibular nerve and the muscles of mastication. Squamous cell carcinoma of the RMT has been treated with primary surgery, primary radiation, and with combinations of surgery, radiotherapy, and chemotherapy with varying success.[3-6]

The objective of the present population-based historical case-series study was to evaluate outcomes in previously untreated patients with squamous cell carcinoma of the RMT and to assess the impact of different treatment modalities on recurrence and survival.

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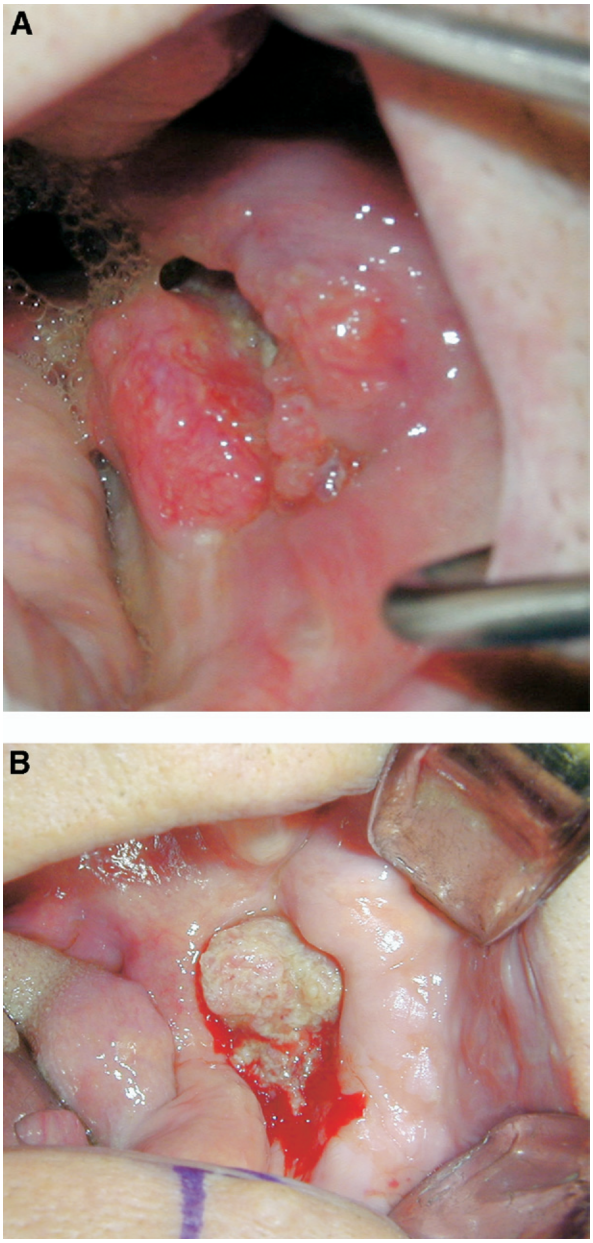

Fig. 1. **A,** Clinical appearance of squamous cell carcinoma of the retromolar trigone at presentation. **B,** Clinical appearance of squamous cell carcinoma of the retromolar trigone at biopsy.

MATERIALS AND METHODS

The charts of 88 patients registered with squamous cell carcinoma of the RMT in the Province of Manitoba, Canada, from January 1975 to January 2004 were evaluated. Approval had been obtained to review these records from the University of Manitoba as part of a protocol entitled "A Quality Management Program for Head and Neck Oncology" (protocol reference no. H2005:071).

Twelve patients were excluded from the study. This was because of incorrect site coding (n = 3), insufficient clinical data (n = 6), or pathology report absent or

Table I. Patient demographics, squamous cell carcinoma of retromolar trigone

Male, n (%)	56 (74%)
Female, n (%)	20 (26%)
Age at presentation, yrs	67.26 ± 10.3
Tobacco and/or alcohol use, n (%)	66 (86%)

Table II. Stage of squamous cell carcinoma of retromolar trigone at diagnosis and survival

Stage of disease	*At diagnosis, n*	*5-year survival*
I	8	75%
II	25	57%
III	12	56%
IV	29	38%

inconsistent with squamous cell carcinoma (n = 3). Seventy-six cases of biopsy-proven previously untreated squamous cell carcinoma of the RMT were identified. One patient presented with bilateral disease 10 years apart. This patient was considered as 2 distinct cases.

Tumor staging was done using clinical data recorded at the time of initial assessment of each patient according to the TNM (tumor, node, and metastasis) classification system of the International Union Against Cancer, 2002.[7] After appropriate merges and data transformation, statistical analysis was done using SPSS software (SPSS, Chicago, IL). Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and percentage (%) and sample size (n) for categoric variables. The comparison between the study groups was done for baseline characteristics using Pearson chi-squared, with continuity correction when appropriate, or Fisher exact test for categoric variables and *t* test or Mann-Whitney *U* test for continuous variables. Kaplan-Meier curves[8] comparing time-to-success (survival) probabilities between the 2 study groups, using the log rank test, were used.

RESULTS

There were 56 men and 20 women, with a mean age of 67.22 ± 10.3 years. Tobacco use, alcohol use, or a combination of both was documented in 66 patients (86%; Table I). Diabetes, hypertension and ischemic heart disease were the most common comorbidities recorded. Twenty-three patients had 34 second primary tumors, of which 62% were synchronous and 55% involved the upper aerodigestive tract.

Eight patients had stage I lesions, whereas 25, 12, and 29 patients had stage II, III, and IV disease respectively (Table II). Two patients were not staged. Twenty-eight patients (36%) had clinically positive nodes at the time of presentation.

Twelve patients were treated with a palliative intent. Surgery was used as the primary treatment modality in

20 patients (26%). Fifteen patients received postoperative radiotherapy. Radiotherapy was used with curative intent in 29 patients (39.5%). Three of these patients had a neck dissection for persistent disease.

Intraoral excision of the primary tumor was performed in 5 patients, whereas the remainder required a cheek flap for exposure. Thirty-two patients underwent mandibular resection, either a marginal resection (n = 10) or segmental mandibulectomy (n = 22). Primary closure was possible in 11 patients. Margins on permanent section were clear in 18 patients, close (within 2 mm) in 8, and involved in 7. Radiation therapy as a primary treatment modality or as adjunctive treatment was delivered by conventional fractionation at a dose ranging from 4,350 to 6,600 cGy.

Twenty-nine patients were managed with neck dissection alone. Ten patients were treated with neck dissection and adjunctive radiotherapy. Thirty-seven patients were treated with radiation alone.

Twenty-eight patients failed treatment, 18 (64%) at the primary site, 3 (10.7%) in the neck, 2 (7%) at the primary site and in the neck. Four patients had distant metastasis, and the site of failure was not documented in 1 patient.

The overall median survival time was greater than 60 months, and 51.4% of the patients survived the 5-year period. When disease-specific survival was considered, 67.7% of the patients survived the 5-year period and median survival time was still above 60 months. The median disease-free survival was 60 months, and 40.3% of the patients survived 5 years.

There was no statistically significant difference between stage of disease and overall survival. Five-year overall survival rates were 75%, 57%, 56%, and 38% for stages I, II, III, and IV, respectively (P = .2230; Fig. 2). Five-year overall survival rates for patients with N0 and N+ neck disease were 55% and 47.5%, respectively (P = .5712). The 5-year overall survival by treatment modality for patients treated with surgery alone was 64%, with surgery and radiotherapy 57%, and 45% when radiation was elected as a single treatment modality (P = .1260). The 5-year overall survival for patients with clear, close (within 2 mm), or involved surgical margins was 68%, 83%, and 0.0%, respectively (P = .0270).

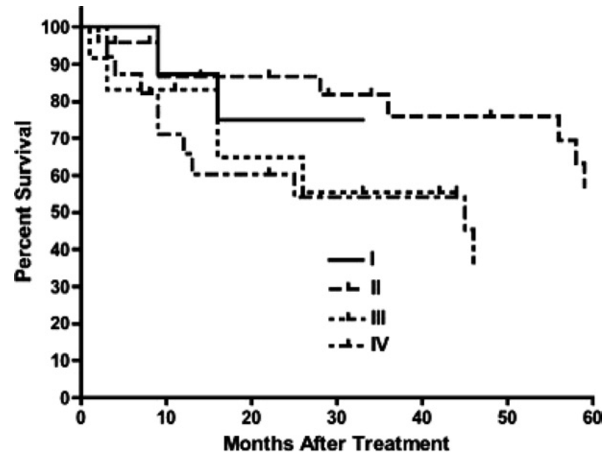

Fig. 2. Overall survival at 5 years by stage of disease at presentation, using Kaplan-Meier analysis.

DISCUSSION

This series of 76 patients with RMT squamous cell carcinoma is comparable to most series of oral cancer in many respects, including age and gender distribution, etiologic factors, and incidence of second primaries. However, in contrast to other series this is a population-based study, describing events over a decade within a well defined geographic boundary, i.e., the Province of Manitoba with a population of 1.5 million.

The authors have developed the clinical impression that patients with early-stage disease of the RMT fail treatment more frequently than observed with similar-staged lesions of the tongue and floor of mouth. Survival of greater than 80% has been reported for early-staged lesions of the tongue and floor of mouth.[9-13]

The previously reported prognosis for squamous cell carcinoma of the RMT is relatively poor, with overall survival ranging from 26% to 80%.[3-6,14-17] Unlike the earlier studies, the overall survival of 51.4% in the present series does not reflect a selection bias for patients and initial treatment modality, such as radical surgery[3] or treatment with radiation alone.[5,14,15] The outcome reported in this study includes all patients managed specifically with squamous cell carcinoma of the RMT.

Clinical stage and survival did not show a significant correlation in the present review. The lack of significance may be a function of the small sample number in each of the subdivided groups. Although Kowalski et al.[3] reported similar findings, other investigators[15,16] have shown a significant influence on stage and survival with both univariate and multivariate analysis.

The initial treatment modality did not affect survival in the present series, which is again consistent with previous reports.[3-5] Surgery seems to have the best survival rate, even if this is not statistically significant. The lack of success may have been due to the small sample number in each treated group. More recent reports of treatment outcomes for squamous cell carcinoma of the RMT suggest that survival is improved with surgery followed by adjunctive radiotherapy.[2,14,16]

The surgical margin status impacted local-regional treatment failure, as reflected by a significant decrease in overall survival with positive margins. This was the only significant predictor of outcome in the present series. This is consistent with some previous reports involving other sites and types of oral cancer.[18,19] However, the margin status was not found to predict survival in some other series.[3,14] This outcome was attributed to the use of postoperative radiotherapy by one investigator.[14]

The lack of concordance between studies with respect to prognostic factors for squamous cell carcinoma of the RMT again reflects small sample sizes with differences in patient selection. Larger multicenter population-based studies using appropriate multivariate models are necessary to resolve these issues.

There is no agreement on the optimal management of these tumors. Early reports[20] recommended surgical treatment over radiotherapy. Kowalski et al.[3] described their experience with extended "commando" operations in 114 patients with or without postoperative radiation and reported a 5-year absolute survival rate of 55.3%. They concluded that adjunctive radiotherapy improved local and regional control.[3] The experience reviewed by Byers et al.[4] in 1984 showed a recurrence rate of 16% in patients treated with radiation therapy alone and 18% in patients treated with postoperative radiation. The 5-year absolute survival was 26%. In another report from the same institution, Lo et al.[5] reviewed experience with irradiation of the anterior faucial pillar and the RMT. The 5-year determinant survival was 83%. In a more recent study Hao et al.[17] reported a 5-year actuarial survival of 60.6% in 50 patients treated with surgery, with 24 receiving adjuvant therapy.

Huang et al.,[14] in their review of 65 patients, showed a 5-year disease-free survival of 31% with radiation alone, compared with 90% and 63% with surgery and pre- or postoperative radiation, respectively. Those authors recommended combined surgery and radiotherapy for all stages of disease. The most recent review by Mendenhall et al.[16] reported 5-year overall survivals of 40% and 56% in 35 patients managed with radiation alone and 64 managed with surgery and radiotherapy, respectively. Using a multivariate analysis they found the stage ($P = .0476$) and the treatment modality ($P = .0098$) to be significant predictors of survival. One other study has shown improved survival with the addition of chemotherapy to surgery and radiation.[5]

The optimal management of squamous cell carcinoma of the RMT cannot be determined from this or any other single review. When considering relatively uncommon tumors such as squamous cell carcinoma of the RMT, there is a need for the head and neck oncology community to pool population-based outcome data to establish accurate prognostic indicators.

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Treatment outcomes in squamous cell carcinoma of the maxillary alveolus and palate: a population-based study

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Objective. This population-based historical cohort study evaluates the treatment outcomes of primary squamous cell carcinoma of the maxillary alveolus and hard palate.
Methods. A historical cohort of 37 cases of previously untreated biopsy-proven squamous cell carcinoma of the upper jaw registered in the Province of Manitoba from January 1975 to January 2004 was analyzed.
Results. The tumor epicenter involved the maxillary alveolus in 26 patients and the hard palate in 11 patients. The mean age of the study population was 72.8 years and 67% were women with a documented tobacco use rate of 50%. Forty-one percent had stage I or II disease, 51% stage III or IV, and 8% could not be staged. Treatment included radiotherapy as a single modality (13.5%), surgery (38%), surgery and radiotherapy (24%), and palliative treatment (24%). Local recurrence was observed in 10 patients with 6 failing at the primary site. The absolute and disease-free survival at 5 years was 33% and 62% respectively. The 5-year disease-free survival was 82% for stage I and II and 48% for stage III and IV ($P = .056$). No patient treated with radiotherapy as a single treatment modality survived 5 years. Disease-free survival for patients treated with surgery, and surgery ± radiotherapy, was 69% and 73% at 5 years, respectively ($P = .001$).
Conclusions. Squamous cell carcinoma of the maxillary alveolus and palate differs from other oral cancers in that the patients are relatively older with a slight female predilection. Treatment with surgery, with or without radiotherapy, appears to improve disease control. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:750-4)**

Squamous cell carcinoma (SCC) of the hard palate and maxillary alveolar ridge could be considered as 1 site since the 2 areas are adjacent anatomically and share similar clinical presentations and management. These are relatively uncommon oral cancers, with a reported incidence ranging from 0.5% to 2.0%.[1,2] Many other investigators have even considered SCC of the maxillary and mandibular alveolar ridges as similar entities.[1,3-5] However, the behavior and management of SCC involving the maxillary and mandibular alveolar ridges is different (Fig. 1, *A-D*), and therefore the interpretation of their results if combined may be difficult. Other publications have not only compared and contrasted SCC of these subsites but have included other tumors of non–squamous cell origin such as salivary gland neoplasms.[6,7] This study examines treatment outcomes in a population-based cohort of patients solely with primary SCC limited to the maxillary alveolus or hard palate.

MATERIALS AND METHODS

The records of 62 patients diagnosed with SCC of the upper jaw and registered in the Province of Manitoba from January 1975 to January 2004 were evaluated. Approval had been obtained to review these records

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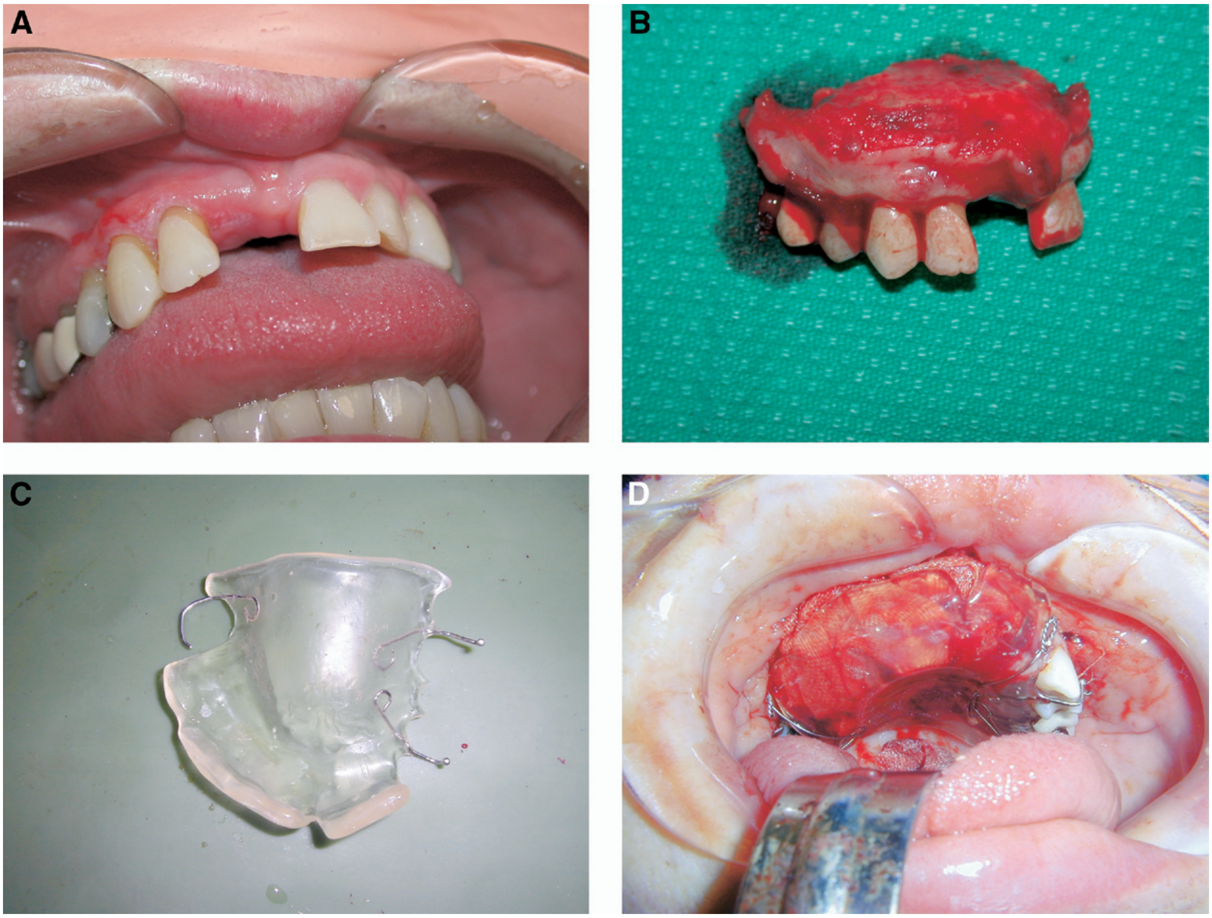

Fig 1. **A,** Stage I squamous cell carcinoma lesion affecting labial aspect of right anterior maxillary alveolus. **B,** Right anterior maxillary alveolus resected en bloc with teeth. **C,** Maxillary resections were managed with a stent fabricated preoperatively to obdurate the defects with oral nasal or oral antral communications immediately after resection. **D,** Stent secured in situ holding in pack and obturating any oral-nasal or oral-antral communications.

from the University of Manitoba as part of a protocol entitled "A Quality Management Program for Head and Neck Oncology" Protocol Reference Number: H2005: 071. Patients were excluded for the following reasons: incorrect site coding (n = 6), insufficient clinical data (n = 2), other pathology (n = 16), and patients seen in consultation only (n = 1). There were 37 cases of biopsy-proven and previously untreated SCC of the maxillary alveolus and hard palate. Staging was done using clinical data recorded at the time of the initial assessment of each patient according to the TNM (tumor, node, and metastasis) classification system of the International Union Against Cancer, 2002.[8]

After appropriate merges and data transformation, statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL). Descriptive statistics are presented as mean ± standard deviation (SD) for continuous variables, percentage (%), and sample size (n) for categorical variables. The comparison between the study groups was done according to baseline characteristics using the Pearson chi-square test with continuous correction when appropriate, Fisher's exact test for categorical variables, and *t* tests or Mann-Whitney *U* test for continuous variables. Kaplan-Meier[9] curves were used to compare time-to-success or survival probabilities between the different study groups using the Log-rank test.

RESULTS

The tumor epicenter was found to involve the maxillary alveolar ridge in 26 patients and the hard palate in the remaining 11 patients (Fig. 2). There were 12 males and 25 females, with a mean age of 72.8 years (SD 12.1). Tobacco, alcohol consumption, or a combination of both was documented in 19 (50%) patients. One patient was a reverse cigarette smoker. Diabetes, hy-

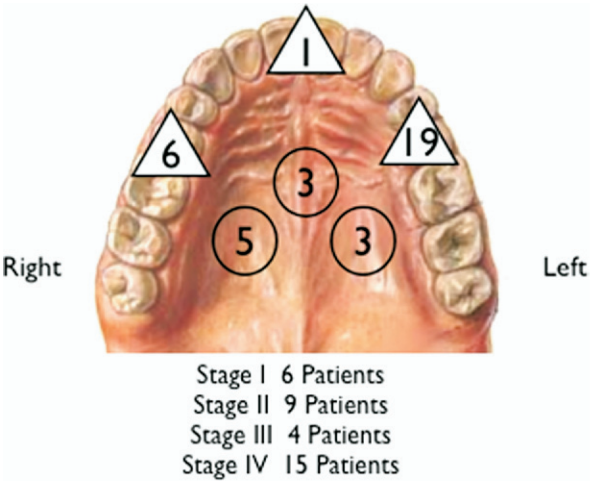

Fig 2. Diagramatic representation of the distribution of the location of the epicenters of the 37 cases of squamous cell carcinoma of the maxillary alveolus and palate reviewed in this case series. Maxillary alveolus represented by triangles; hard palate represented by circles.

Table I. Stage of disease at time of presentation

Stage of disease	*No. of patients**
Stage I	6
Stage II	9
Stage III	4
Stage IV	15

*Three patients were not staged.

Table II. Treatment by stage

Stage of disease	*Surgery*	*Radiotherapy*	*Combination*
Stage I	5	0	0
Stage II	7	1	1
Stage III	0	1	3
Stage IV	2	1	6*
Not Staged	0	2	0

Eight patients were treated with palliative intent.
*One patient was treated with radiation and chemotherapy.

pertension, and ischemic heart disease were the most common comorbidities recorded. Eight of the patients had a total of 11second primary tumors, of which 42% were synchronous and involved the upper aerodigestive tract. Fourteen patients (38%) had pain as the major presenting symptom. Six patients had stage I lesions, 9 stage II, 4 stage III, and 15 patients stage IV. Three patients could not be staged. Seven patients (19%) had clinically positive nodes at the time of presentation (Table I).

Eight patients (21.6%) were treated with a solely palliative intent. Surgery was used as the primary treatment modality in 23 patients with 9 of these patients receiving postoperative radiotherapy. Radiotherapy was used as a single treatment modality in 5 patients (13.5%). One patient was treated with radiotherapy and chemotherapy (Table II). In the 23 patients treated with surgery a transoral excision was used in 11 cases. In 11 patients a cheek flap was deemed necessary for adequate exposure. An operative report was not identified in 1 patient. Margins on permanent section were found to be clear in 16 patients, close or within 2 mm in 3 of the patients, and involved in 4 patients. Radiation therapy, whether used as an adjunctive or as a primary treatment modality, was delivered by conventional fractionation at doses ranging from 4125 to 7000 CGy. Four of the 7 patients presenting with positive lymph nodes were treated with a curative intent. Two of these patients were treated with radiation alone. In the remaining 25 node-negative patients who were treated with curative intent, the neck was treated electively in 2.

Ten of the 29 patients treated with curative intent failed treatment with 6 failing at the primary site and 4 failing in the neck. The absolute and disease-free survival at 5 years was 33% and 62% respectively (Figs. 3 and 4). The 5-year disease-free survival (Fig. 5) was 82% for stage I and II and 48% for stage III and IV ($P = .056$). The initial treatment modality, whether surgery, radiotherapy, or a combination of both, significantly influenced the 5-year survival rate ($P = .001$). No patient treated with radiotherapy as a single treatment modality survived 5 years or longer. The 5-year disease- free survival for patients treated with surgery alone, and a combination of surgery and radiotherapy was 69% and 73% respectively. Margin status did not affect survival in any of the cases with involved margins.

DISCUSSION

Squamous cell carcinoma of the maxillary alveolus and hard palate is relatively uncommon in Western society.[10-12] Petruzzelli and Mayers[13] noted that neoplasias, both SCC and non-SCC, of the upper jaw constitute only 2% of all head and neck malignancies and 10% of oral cancers. The lesions appear to be considerably more common in India, accounting for 40% to 55% of the oropharyngeal cancers.[14,15] The relatively low numbers of these tumors is the most likely reason these lesions are often grouped and reported together with other sites such as the mandibular alveolus[3,5] and soft palate[1,6] or combined with salivary gland tumors.[1,5] In contrast to most other reports, this

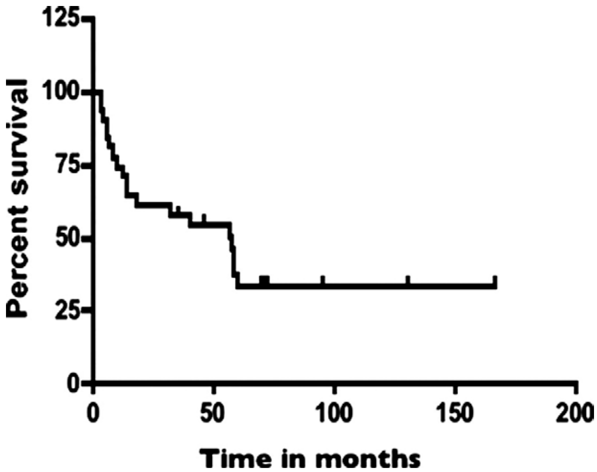

Fig 3. Kaplan-Meier survival curves showing 5-year overall survival.

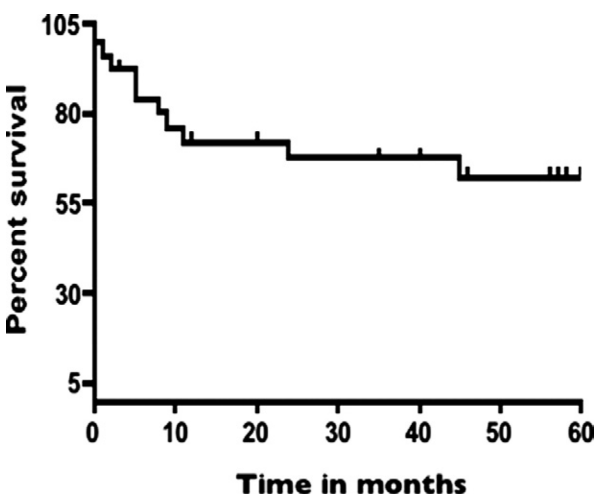

Fig 4. Kaplan-Meier survival curves showing 5-year overall disease-free survival.

study examines treatment outcomes in a site that is anatomically specific and is pathologically limited to squamous cell carcinoma of the maxillary alveolus and hard palate in a population-based historical cohort.

The anatomical characteristics of the maxillary alveolar ridge and hard palate are similar as together they form the roof of the oral cavity and the floor of the nasal cavity and maxillary sinus. Full-thickness resection of the structures involved by tumor at this site will result in oronasal and oral-antral communication, a problem unique to this site. This unique anatomic relationship makes the radiographic work-up with computed tomography (CT) scans and magnetic resonance imaging (MRI) scans crucial to determine tumor extent and

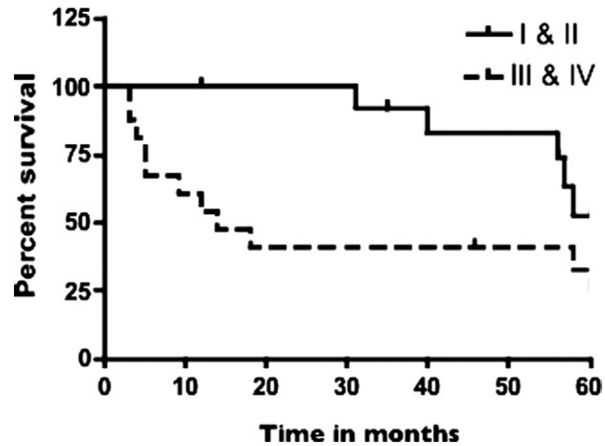

Fig 5. Kaplan-Meier survival curves showing 5-year survival related to stage of disease.

stage. This radiographic visualization ultimately helps decide the staging, the extent of surgical resection, and the use of other modalities of treatment.

Therefore, the clinical presentation, the surgical management, and reconstructive considerations including the management of oronasal and oral-antral communication with immediate obturation, are similar for these sites (Fig. 1, *A* to *D*). From a clinical perspective, it is often difficult in advanced tumors to determine the exact epicenter (Fig. 2). The maxillary alveolus and hard palate, in contrast to the remainder of the oral cavity, seem to share a female predilection in this and other reports.[16,17] In searching the literature further, the authors were unable to find reasons for this female predilection as of yet. However, based on the foregoing, the authors feel that it is most appropriate to consider SCC of the upper alveolus and hard palate as a single entity.

The overall or absolute survival of 33% at 5 years reported in this study is relatively low. Reported survival rates for these sites, which range from 21% to 76%,[1,5] are difficult to interpret, as they are often grouped to include other sites and other pathological entities such as salivary gland tumors. The Improved disease-free survival at 5 years of 62% reported in the current study reflects the influence of advanced age of the patients with significant comorbidities on overall survival. These considerations as well as the frequency of stage IV disease (40%), account for the relatively large number of patients not amenable to treatment with curative intent.

Margin status did not affect survival or outcome in any of the cases with involved margins. The reality is that this is a study of only 37 cases in a rare site and the authors did not feel comfortable drawing conclusions from such a small sample.

The number of participants in this study is too small to examine prognostic factors in detail. In this report there was a trend toward decreased survival with advanced stage of disease as observed in other series.[16,17] Yokoo et al.[18] were unable to correlate stage of disease with prognosis. In their series, 80% of patients had stage IV tumors. They proposed a new classification system dependent upon the involvement of the maxillary sinus or nasal floor. The authors of the present study observed improved survival in patients treated with surgery. Arguments in favor of one treatment modality over another in this, and the other series reviewed, are of limited value because of small sample size in the studies.

There seems to be better prognosis for Stage III and IV lesions at this site compared to the late stages at other oropharyngeal sites. This trend was confirmed in other series.[16-18] The reasons for this are unknown and not apparent in the literature. The authors feel that this may be because of differences in lymphatic drainage at the maxillary alveolar and palatal sites when compared to other oropharyngeal sites. This tumor is more prevalent in India and these numbers may also represent some geographic differences potentially due to differences in social habits such as reverse cigarette smoking. The authors feel that the numbers in the current study are too small to be able to make further conclusions at this time.

In conclusion, squamous cell carcinoma of the maxillary alveolar ridge and hard palate differs from other oral cancers in several aspects. SCC tends to occur at these sites in a relatively older population with a female predilection. A relatively high number of patients were not amenable to treatment with curative intent. Treatment with surgery, with or without radiotherapy, appears to improve disease control. A future prospective multicenter study with a larger cohort of patients may help to answer questions regarding the prognosis of treatment related to the specific stages of this disease.

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Relationship of the maxillary artery and lateral pterygoid muscle in a caucasian sample

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Objective. Several studies have investigated the relationship between the maxillary artery and the lateral pterygoid muscle, yet controversy still exists regarding this relationship. The purpose of this study was to re-examine this relationship in a sample of caucasian cadavers in Canada.

Study design. All soft tissues were removed from the mandibles of 44 caucasian cadavers. Mandibular osteotomies were performed to expose the infratemporal fossa and to dissect the maxillary artery bilaterally. Once accomplished, the relationship of the second part of the maxillary artery to the lower head of the lateral pterygoid muscle, and any variation in symmetry, was recorded.

Results. In the majority of cases (30/44), the artery was found lateral to the lower head of the lateral pterygoid muscle (71% in men and 65% in women). The maxillary artery was found medial to the lower head of the lateral pterygoid muscle in only 14 of the cases (29% in men and 35% in women). No variations in the course of the maxillary artery were noted between the 2 sides and between both genders.

Conclusions. This study shows that the lateral or superficial course of the maxillary artery relative to the lower head of the lateral pterygoid muscle is more prevalent than the medial or deep course. This is in agreement with the majority of previously published results. There were no variations in the course of the artery between the 2 sides of the same cadaver or between cadavers of both genders. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:32-6)**

The topographic relations of the second part of the human maxillary artery in the infratemporal fossa have been studied since the late nineteenth century.[1-7] A number of reports showed the course of the second part of human maxillary artery in the infratemporal fossa to be variable.[3,8] Understanding the anatomy of the human maxillary artery and its branches in the infratemporal fossa is a prerequisite for many surgical and clinical procedures. For instance, tumors involving the cavernous sinus and the floor of the middle cranial fossa, such as meningiomas and trigeminal schwannomas, may extend into the infratemporal fossa. Other tumors originating in the nasopharynx such as angiofibromas, in the maxillary sinus such as carcinomas, and in the parotid gland such as adenoid cystic carcinoma can also invade the infratemporal fossa. In clinical dentistry, mandibular block techniques, including the Gow Gates and Vazirani-Akinosi, are commonly used to achieve anesthesia of the mandibular nerve. Careful administration of the local anesthetic is necessary to avoid intra-arterial injection into the maxillary artery.[2,9] Knowledge of the anatomy of the human maxillary artery in the infratemporal fossa is important to dentists, surgeons, and interventional radiologists.[10]

The maxillary artery arises as 1 of the 2 terminal branches of the external carotid artery behind the neck of the mandibular condyle, deep to or within the substance of the parotid gland.[11,12] From its origin, the course of the maxillary artery is divided into 3 parts. The first or "mandibular" part runs nearly horizontal and deep to the neck of the mandibular condyle, and superficial to the sphenomandibular ligament during its course to the lower border of the lower head of lateral pterygoid muscle in the infratemporal fossa. The second or "pterygoid" part runs obliquely forward either superficial or deep to the lower head of the lateral

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pterygoid muscle. At this site, it is embedded into the pterygoid venous plexus. Finally, the third or "pterygopalatine" part disappears from view by diving between the two heads of lateral pterygoid muscle to reach the pterygopalataine fossa via the pterygomaxillary fissure. There, it gives off several branches that accompany the corresponding branches of the maxillary nerve.

The variable course of the second part of the maxillary artery has stimulated a considerable number of reports.[3,8] Lauber[5] found only 16 arteries (8.5%) out of 200 cases to be superficial to the lower head of the lateral pterygoid muscle. However, the superficial position of the maxillary artery seemed to occur in about 54%-70% of the cases in Caucasians[3,4,6,7,13] and in 69% in Africans.[4] Adachi[1] stated that the superficial position of the second part of the maxillary artery occurred with highest frequency in the Japanese population and referred to this as a "racial difference." In support of this idea, Laskar et al.[4] found the artery deep to the muscle in 46% of 147 cases in Caucasians and in 31% of 61 cases in Africans, and therefore they coined the term "racial blood vessel." In the present study the authors have revisited the relationship of the second part of the maxillary artery to the lateral pterygoid muscle in a sample of the Caucasian population in Canada. The relationship of maxillary artery to the mandibular nerve and its branches was not a subject of this study.

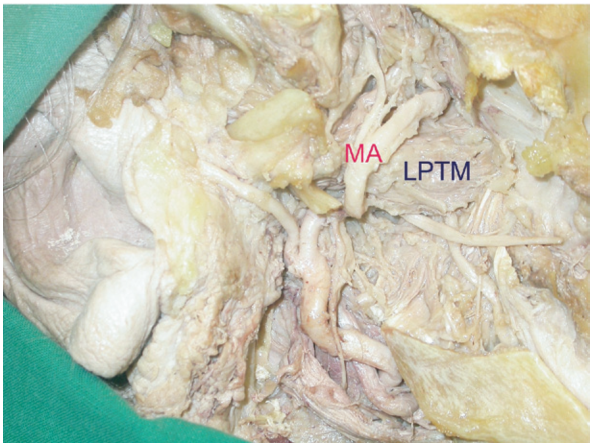

Fig. 1. The mandible has been removed, after severing the tendon of the temporalis muscle to expose the underlying tissue. The second portion of the maxillary artery (MA) has been dissected to reveal its relationship to the lower head of the lateral pterygoid muscle (LPTM). The superficial, or lateral, position of the second portion of the MA relative to the lower head of the LPTM is seen in this specimen.

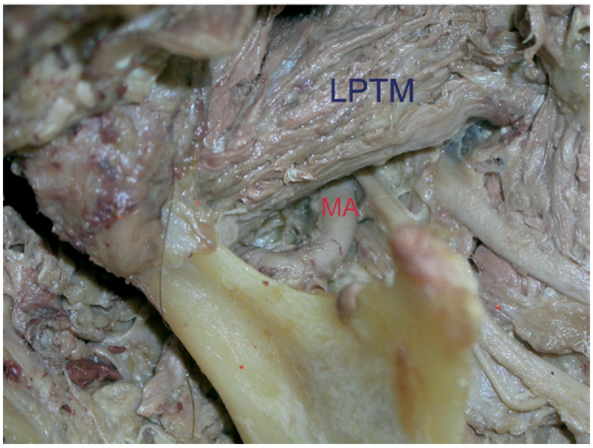

Fig. 2. This specimen shows the deep, or medial, position of the second part of the maxillary artery (MA) to the lower head of the lateral pterygoid muscle (LPTM).

MATERIAL AND METHODS

The present study is based on investigations in 44 cadavers (21 men and 23 women) that were embalmed and preserved in 2% formalin in the gross anatomy dissection laboratory at the University of Manitoba. All specimens were caucasian of known age and gender.

The maxillary arteries were dissected bilaterally using a lateral infratemporal approach. The covering soft tissues, including the skin, fascial layers, and superficial portion of the parotid gland and masseter and temporalis muscles, were removed. The lateral surface of the ramus of the mandible was exposed along with the external carotid artery and the origin of the maxillary artery. This approach also exposed the mandibular condyles. Using an angled oscillating saw (Stryker, Kalamazoo, MI), the zygomatic arches were removed and the mandibles were osteotomized at the neck of the condyles and at the symphysis menti. The attachment of the lateral pterygoid muscle to the pterygoid fovea and the tempromandibular joint (TMJ) was preserved. The mandible was then removed from its muscular attachments, including the medial pterygoid, anterior belly of digastric, mylohyoid, geniohyoid, and genioglossus muscles, without damaging any underlying tissues (Fig. 1). These procedures were also carried out on the contralateral side.

Careful dissection of the first and second parts of maxillary artery was performed so that the intimate relation of the second part of maxillary artery to the lower head of lateral pterygoid could be visualized. The deep (Fig. 2) or superficial location (Fig. 1) of the second part of the maxillary artery to the lower head of the lateral pterygoid muscle was recorded in every specimen. This relationship and any variations in sym-

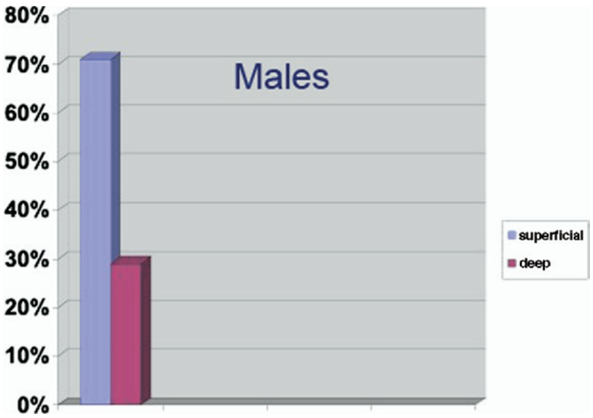

Fig. 3. The percentages of the superficial and deep positions of the maxillary artery in 21 male specimens (P = .052).

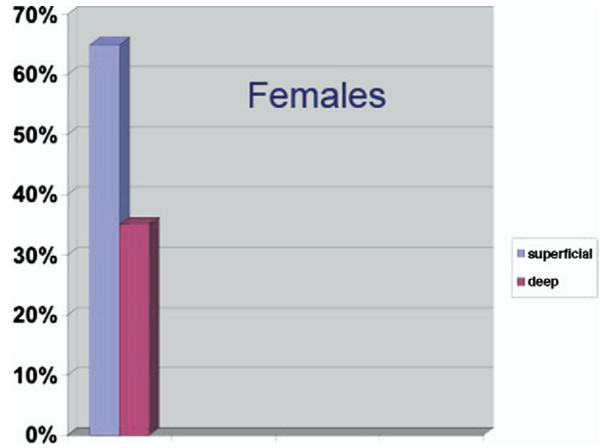

Fig. 4. The percentages of the superficial and deep positions of the maxillary artery in 23 female specimens (P = .117).

metry were checked and documented. Photographs were taken using a digital camera (Coolpix 4500; Nikon, Tokyo, Japan). The information collected was statistically analyzed using the 2-tailed binomial test assuming a 50% chance that the maxillary artery will be superficial or deep to the inferior head of the lateral pterygoid muscle.

RESULTS

Superficial (lateral) course of the maxillary artery to the lower head of the lateral pterygoid muscle

The lateral or superficial position of the second part of the maxillary artery in relation to the lower head of the lateral pterygoid muscle was found in 68% of all the specimens examined. In the male cadavers, the second part of the maxillary artery was found to be superficial in 71% of the total number of cases (P = .052). In the female cadavers, the artery was found to be superficial to the lower head of the lateral pterygoid muscle in 65% of the total number of cases (P = .117). There was no statistically significant variation in the course of the maxillary artery between both sides of the same cadaver and between genders (Figs. 3 and 4).

Deep (medial) course of the maxillary artery to the lower head of lateral pterygoid muscle

The frequency of the deep (medial) course of the second part of the maxillary artery was relatively low. The maxillary artery was found to run deep to the lower head of the lateral pterygoid muscle in only 32% of all the cases. In the male cadavers, the incidence was 29%, and in the female cadavers it was 35% (Figs. 3 and 4). Although there was a trend for female cadavers to display the deep course of the maxillary artery more often than males, this difference was not statistically significant. Similarly, there was no statistically significant variation in the deep course of maxillary artery between the two sides in the same specimen and between genders.

DISCUSSION

Understanding the course of the maxillary artery in the infratemporal fossa with its variation is of potential interest to many practitioners. For instance, tumors arising or extending into the infratemporal fossa via foramen ovale or foramen rotundum, such as juvenile nasopharyngeal angiofibromas, are commonly excised by lateral cranial base approaches (Fisch type C)[8,11] or subtemporal/infratemporal approaches.[13-17] In these approaches, the entire contents of the infratemporal fossa are exposed, including the maxillary artery which may be greatly susceptible to damage or sacrifice, depending on the extent of the surgery and the size of the tumor. Therefore, knowing the course of the maxillary artery and its variations will aid in surgical planning and in minimizing intraoperative or postoperative hemorrhage.

Many orthognathic and TMJ surgical procedures are performed in close proximity to the maxillary artery in the infratemporal fossa. Mandibular osteotomies, such as intraoral vertical ramus osteotomy or bilateral sagittal split osteotomy, are commonly performed to correct dentofacial deformities.[18] Open TMJ procedures using the preauricular approach are relatively commonly used. These surgical procedures or approaches have been developed to improve safety to minimize or prevent damage to vital anatomic structures such as the maxillary artery. Avoidance of the maxillary artery or one of its branches is necessary to prevent extensive intraoperative or postoperative hemorrhage.[18,19]

In clinical dentistry, mandibular blocks,[12] such as

Gow-Gates or Vazirani-Akinosi, are very commonly used techniques to deliver local anesthetic agents before many dental procedures. The site of injection is extremely close to the branches of the maxillary artery, which may result in undesirable consequences, such as intrarterial injection or hematoma.[20] The clinician must be fully aware of the course of the maxillary artery and its variations to prevent the side effects from intra-arterial local anesthetic injection.

The course of the maxillary artery in relation to the inferior head of the lateral pterygoid muscle has been a controversial point. As a result, a number of studies have been conducted to investigate this mutual relationship. A review of the literature shows that many authors found the maxillary artery superficial to the lower head of lateral pterygoid muscle. This finding ranged between 54% and 70%.[4,6,7,9,21,22] Moreover, Adachi[1] found a higher frequency of superficiality (93%) in the Japanese population, raising the possibility of racial differences. However, Lauber's[5] investigation showed only 8.5% of the Caucasian population with a superficial maxillary artery. In the present study, the relationship of maxillary artery to the lower head of the lateral pterygoid muscle was generally similar to that of other studies. On one hand, a trend was noted in the lateral course of the maxillary artery relative to the lower head of the lateral pterygoid muscle to be more common in men (71%) than in women (65%), supporting other data in the literature.[4,6,7,9,21,22] On the other hand, the medial course was less common in men (29%) than in women (35%) in the present study. However, the course of the maxillary artery in relation to the lower head of the lateral pterygoid was symmetrical in all of the present specimens. This is not in agreement with the report by Pretterklieber et al.[23] That study is the only one that shows asymmetry to exist in the course of the maxillary artery between the 2 sides in the same specimen. That finding of Pretterklieber et al. seems questionable because there is no other supporting work in the literature.

Many authors have attempted to explain the potential factors that determine the position of maxillary artery relative to the lateral pterygoid muscle in the infratemporal fossa. However, craniometric analysis, including facial height, cranial breadth or length, and cephalic index, did not reveal any correlation between the variable position of the maxillary artery and the measured craniometric parameters.[9,21-26] In another study by Lurje,[27] the lateral course of the maxillary artery was found to be more common in brachycephalic and mesocephalic individuals. However, that study lacked any statistical evaluation and was contradicted by other studies such as that of Laskar et al.[4] One theory, the metabolic hypothesis,[28] was proposed to explain the potential factors involved in angiogenesis and the vascularization of growing tissues. However, it failed to explain the factors responsible for variation in the position of the second part of the maxillary artery relative to the lateral pterygoid muscle.

In conclusion, the present study confirms some of the earlier findings concerning the more common superficial position of the maxillary artery in relation to the lateral pterygoid muscle. However, the findings that there was a trend for the deeper course of the second part of the maxillary artery to be slightly more common in women than in men and that there was no evidence of asymmetry in the course of the artery within the 2 sides of the same specimen were unique to this study. The mechanism responsible for determining the relative position of the artery to the lateral pterygoid muscle is still unknown. The present study helps to begin to define the question of the effect of ethnicity on the relative position of the maxillary artery to the inferior head of the lateral pterygoid muscle by studying a Caucasian population from Canada. Comparison with future studies in other ethnic groups[19] will further help to answer this question.

The relationship between the maxillary artery and the lateral pterygoid muscle may be important during major facial reconstruction, cleft craniofacial reconstruction, cancer surgery, and surgery to the TMJ. The anatomy of the terminal end of the maxillary artery should be kept in mind during surgical dissection.

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Clinical Paper
Head and Neck Oncology

Clinical observations of the anatomy and function of the marginal mandibular nerve☆

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R. W. Nason, A. Binahmed, M. G. Torchia, J. Thliversis: Clinical observations of the anatomy and function of the marginal mandibular nerve. Int. J. Oral Maxillofac. Surg. 2007; 36: 712–715.

Abstract. The objective of this study was to assess the anatomical variation of the marginal mandibular nerve, and evaluate the risk of nerve malfunction after neck dissection. The method involved clinical assessment of the anatomy and function of the marginal mandibular nerve in 133 neck dissections. When the neck was extended the nerve was displaced in an anterior and downward direction with the lowest point 1.25 ± 0.7 cm below the mandible between the posterior and anterior facial veins. The nerve was >1 cm below the lower border of the mandible in 54% of dissections. When the intent was to preserve the nerve, dysfunction was observed in 16 of 101 dissections (16%). The incidence of marginal mandibular nerve dysfunction following neck dissection is comparable to that observed following submandibular gland excision for benign disease. Placement of incisions 2 cm below the lower border of the mandible will put the nerve at risk in a significant number of patients.

Key words: marginal mandibular nerve; neck dissection.

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Injury to the marginal mandibular nerve results in a significant cosmetic deformity. The deformity is caused by interruption of nerve fibers to the depresssor anguli oris and the depressor labii inferioris that results in flattening and inversion of the ipsilateral lower lip and the inability to move the lip downward and laterally. The defect may not be apparent with the face in repose. Elevation of the affected lower lip is evident when the patient smiles, and the asymmetry is most obvious when the patient cries – the 'asymmetric crying facies'[5,11]. The reported incidence of marginal mandibular nerve injury ranges from 0 to 20% following submandibular gland removal[3,4,9]. Injury to the marginal mandibular nerve in the course of a neck dissection has been considered an acceptable outcome[3,5] and the incidence of nerve dysfunction in this context is not reported.

Knowledge of the course and anatomic relations of the marginal mandibular nerve in the upper neck is important in avoiding injury. The nerve is usually described as it relates to the lower border of the mandible and the facial vessels. The seminal work on the surgical anatomy of the marginal mandibular nerve is based on Dingman & Grabb's study[2] of 100 embalmed cadaver facial halves. They described two or more rami of this branch of the facial nerve at the level of the angle of the mandible. In 98% of specimens the nerve passed downward and forward over the surface of the posterior facial vein and more anteriorly the nerve crossed the anterior surface of the anterior facial vein in 100% of specimens. Immediately anterior to the facial vein the branches of the mandibular ramus

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passed superficial, deep or on both surfaces of the facial artery. They tended to be superficial to the artery. It was found that posterior to the facial artery the mandibular ramus ran above the inferior border of the mandible in 81% of specimens and in the other 19% the nerve or one or more of its branches ran in an arc 1 cm or less below the inferior border of the mandible. Anterior to the facial artery all branches were above the inferior border of the mandible. Dingman & Grabb's[2] observations and other cadaver dissections[12] imply that incisions placed 2 cm below the lower border of the mandible will avoid injury to the nerve in all instances. Clinical observations[1,6] suggest that the nerve is consistently below the inferior border of the mandible. Baker & Conley[1] noted that in individuals with lax and atrophic tissue the nerve could be as low as 3–4 cm below this point.

This study reports clinical observations on the surgical relations of the marginal mandibular nerve at the time of neck dissection. The incidence of nerve dysfunction following neck dissection is documented.

Methods

Clinical observations of the anatomy and function of the marginal mandibular nerve were recorded in 133 neck dissections in 121 patients. There were 78 males and 48 females with a mean age of 54.31 ± 17.0 years. The neck dissections were done for squamous cell carcinoma ($n = 93$), thyroid cancer ($n = 21$), salivary gland malignancy ($n = 9$), melanoma ($n = 8$), angiosarcoma ($n = 1$), and Levoise-Bensaud syndrome ($n = 1$). The neck dissections were classified as comprehensive in 72 necks, selective in 59 and extended in 2. Level I nodes were removed in 109 (83%) of the dissections. Twenty-five patients had received radiotherapy prior to the neck dissection.

All patients were positioned with a roll under the shoulders to maintain extension of the neck. Skin incisions in the upper neck were placed in skin creases 2–4 cm below the lower border of the mandible. In general, skin flaps were elevated with sharp dissection in a sub-platysmal plane. When Level I was dissected an attempt was made to identify the marginal mandibular nerve using standard landmarks[2,6,10]. This generally involved observation of the nerve coursing superficial to the anterior facial vein. The distance from the lower border of the mandible to the lowest point of the nerve in the neck was measured. The relationship of the lowest point of the marginal mandibular nerve to the anterior facial vein and posterior facial vein (anterior division of retromandibular vein) was noted. These measurements and relationships were recorded with the head in a neutral position, and in an extended position with downward traction on the investing layer of the deep cervical fascia.

The functional status of the marginal mandibular nerve was recorded at the time of each postoperative visit. The patients were generally followed at intervals of 2–3 months. The average length of follow up was 661.18 days (range: 7–1832 days; median: 541 days). Statistical analysis was performed with a Student's t-test, Chi-square, or multivariate analysis where appropriate.

Table 1. Management of the marginal mandibular nerve in 133 neck dissections

Management intent	Nerve visualized	Nerve not visualized	Total
Preserve	76 (68)	36 (32)	112
Sacrifice	9 (43)	12 (57)	21
Total	85 (64)	48 (36)	133

Numbers in parentheses are percentages.

Results

The marginal mandibular nerve was managed with the intent to preserve function in 112 (84%) necks. The nerve was visualized in 76 (68%) of these patients. A decision to sacrifice the nerve, based on oncological considerations, was made in 21 dissections (Table 1).

Observations on the course and surgical relations of the marginal mandibular nerve were recorded in 85 patients. With the head in neutral position the nerve was at its lowest point 0.31 ± 0.4 cm (range 0.0–1.5 cm) below the inferior border of the mandible in the region of the posterior facial vein (Fig. 1). With the neck extended the nerve was displaced in an anterior and downward direction with the

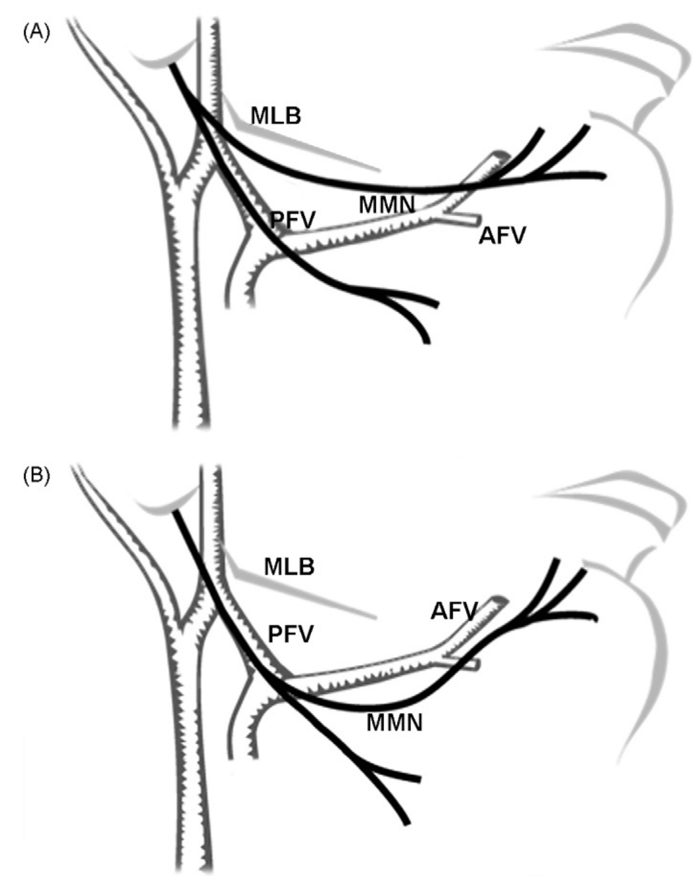

Fig. 1. The relation of the marginal mandibular nerve (MMN) to the lower border of the mandible (MLB), anterior facial vein (AFV) and posterior facial vein (PFV) with the neck in a neutral position (A) and in an extended position (B) with downward traction on the cervical fascia.

Table 2. Distance marginal mandibular nerve identified below the mandible with the neck in neutral and extended position in 78 neck dissections

Distance below mandible (cm)	Neutral	Extended
>1	3 (4)	42 (54)
>2	0 (0)	8 (10)

Numbers in parentheses are percentages.

lowest point 1.25 ± 0.7 cm (range 0–3.0 cm) below the mandible between the posterior and anterior facial veins ($P < 0.01$). In the extended position the nerve was >1 cm below the lower border of the mandible in 42 (54%) and >2 cm in 8 (10%) patients (Table 2).

The functional status of the nerve was recorded following 121 neck dissections. Praxia was recorded in 18 (90%) patients where the nerve was visualized and deliberately divided ($n = 9$) or presumed divided with dissection in a plane superficial to the platysma ($n = 11$) for oncologic reasons. In the remaining 101 patients where the intent was to preserve the nerve, praxia was observed in the immediate postoperative period in 29 and persisted in 16 (16%). Temporary dysfunction of the marginal mandibular nerve had usually resolved by the second or third postoperative visits (3–6 months). Praxia was not observed in the 24 patients where level I lymph nodes were not dissected. The incidence in the 77 patients where a level I dissection was performed with the intent to preserve nerve function was 16/77 (21%). The relationship between nerve dysfunction and clinical and treatment-related factors in this subset is shown in Table 3. The incidence of nerve dysfunction appeared to be higher when the neck dissection followed radiotherapy. This approached, but did not achieve, statistical significance. Visualization of the nerve during neck dissection did not affect the functional outcome. The use of multivariate models did not establish any independent predictors of nerve dysfunction.

Discussion

The complication of marginal mandibular nerve injury following neck dissections for malignant disease has not received much attention. This is not surprising as historically other morbidities of major head and neck resections have overwhelmed this disability. The significance of asymmetry of the lower lip increases as morbidity from other aspects of the treatment is minimized through multimodal treatment plans that incorporate conservative surgical approaches and organ preservation protocols. The frequency of nerve dysfunction observed in this prospective evaluation of neck dissections, is comparable to that reported in retrospective reviews of outcome following excision of the submandibular gland for benign disease. It is recognized that retrospective studies underestimate the true incidence of complications.

This series represents a heterogeneous population of patients with respect to pathological, clinical and treatment-related parameters including the extent of neck dissection. In the cases where praxia of the marginal mandibular nerve was observed following a neck dissection with visualized or presumed division of the nerve, the outcome of the nerve could usually be predicted preoperatively. These patients generally had advanced local or regional disease. Patients where level I nodes were not dissected were included in the functional assessment as the proximal marginal mandibular nerve is exposed to potential traction type injury from retraction to expose high jugulodigastric lymph nodes. The absence of nerve dysfunction in this cohort of patients may be explained by the fact that the nerve is well protected by surrounding soft tissue. When level I was dissected and the intent was to preserve the nerve, the incidence of praxia appeared to be higher after preoperative radiotherapy. The majority of patients in this series were managed surgically within 6–8 weeks of completion of radiotherapy. Tissue planes tended to be edematous, but the anatomy was not distorted. The fact that no independent predictors of nerve dysfunction were identified in patients where level I was dissected suggests that anatomic considerations are paramount in preserving the function of the marginal mandibular nerve.

The anatomy of the marginal mandibular nerve in its vulnerable position in the upper neck is variable between patients. The course and position of the nerve also varies with the position of the head and downward traction on the investing layer of cervical fascia. The dynamic nature of the nerve was evident in this study. This explains, in part, the discrepancies between cadaver studies and clinical observations. Cadaver tissue is contracted and relatively immobile. Of interest, when fresh as opposed to embalmed cadaver material is studied, the nerve is consistently reported below the lower border of the mandible. In a series of 22 fresh cadavers Savary et al.[7] observed the nerve

Table 3. Relationship between clinical and treatment-related factors and the incidence of marginal mandibular nerve dysfunction in 77 patients where level I was dissected with the intent to preserve nerve function

Variable	Praxia	Normal function	*P*-value
Gender			
Male	11 (19.6)	45	0.755
Female	5 (23.8)	16	
Age			
>57	11 (24.4)	34	0.405
≤57	5 (15.6)	27	
Pathology			
SCC	12 (18.5)	53	0.259
Other	4 (33.3)	8	
Preoperative radiotherapy			
Yes	7 (36.8)	12	0.058
No	9 (15.5)	49	
Oral/oropharyngeal resection			
Yes	4 (11.1)	32	0.089
No	12 (29.3)	29	
Level I nodes positive			
Yes	1 (10.0)	9	0.678
No	15 (22.4)	52	
Nerve visualized			
Yes	13 (20.0)	52	0.706
No	3 (25.0)	9	

Numbers in parentheses are percentages. SCC, squamous cell carcinoma.

below the mandible in 63% of specimens posterior to the facial artery and in 27% anterior to the artery. They observed some branches as low as 3–4 cm below the lower border of the mandible. Nelson & Gingrass[6] noted that the marginal mandibular nerve was well below the inferior border of the mandible in almost every instance in fresh cadaver specimens and clinical dissections. Both these reports recommended cervical incisions several centimetres below the inferior border of the mandible. The present study confirms the consistent course of the marginal nerve below the inferior border of the mandible. The observation by Baker & Conley[1] that the nerve is drawn downward when the neck is extended is confirmed. The placement of cervical incisions 2 cm below the lower border of mandible will place the nerve at risk in a significant number of patients.

Detailed anatomic dissections[2,6,8] show that there are often multiple contributions to the marginal mandibular nerve, and that it can be difficult to discern between mandibular and platysmal branches. Dingman & Grabb[2] note that in many specimens fine branches could be seen running along the lower border of the mandible, some up to 2 cm below it. They stated that these branches terminated in and innervated the platysma in all specimens. Nelson & Gingrass[6] argued that these same branches, when followed anteriorly in fresh cadaver specimens and in clinical practice, ascended over the lower border of the mandible to innervate specific lip depressors. They contend that these branches should be identified as mandibular and not cervical branches. Skandalakis et al.[8] describes an anterior ramus of the cervical division of the facial nerve that joins the mandibular ramus to contribute to the innervation of the lower lip. There are also observations that the platysma, innervated by the cervical division of the facial nerve, contributes to depression of the lower lip[11]. Division of the cervical branch of the facial nerve or the platysma can result in a pseudo-paralysis of the marginal mandibular nerve that usually recovers spontaneously. Detailed dissections of the marginal mandibular nerve were not done in the present study. From a practical point of view there is usually a single identifiable nerve ramus coursing superficial to the facial veins that results in asymmetry of the lower lip if divided. Stern[10] indicates that if the nerve does not course above the inferior border of the mandible within 2 cm of the facial vessels it is not the marginal mandibular nerve.

A low cervical incision with a ‘non-visualization’ approach to the marginal mandibular nerve is supported[4,9] for management of benign disease of the submandibular gland. In this study visualization of the nerve during the course of a neck dissection was not associated with a lower incidence of nerve dysfunction. The following technical considerations should minimize injury to the marginal mandibular nerve in the context of a neck dissection. Irrespective of the site of the skin incision, skin flaps should be carefully elevated in a plane immediately deep to the platysma and superficial to the investing layer of deep cervical fascia and marginal mandibular nerve. It is not the level of the skin incision that is important but the level of transection of the investing layer of cervical fascia. Knowledge of the dynamic and variable location of the marginal mandibular nerve relative to the inferior border of the mandible is useful in this regard. The decision to visualize the nerve needs to be individualized. If it is deemed necessary to divide the cervical fascia within 3–4 cm of the inferior border of the mandible it is the authors’ opinion that an attempt should be made to visualize the course of the nerve. The nerve is then preserved or sacrificed based on the oncologic objectives of the procedure. Electrical cautery should be used sparingly, and attention should be directed to avoiding traction or pressure injury from retractors.

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ORAL ONCOLOGY

The clinical significance of the positive surgical margin in oral cancer ☆

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Summary The objective of surgical management of squamous cell carcinoma of the oral cavity is adequate resection with a clear margin. This study examines the significance of the positive surgical margin. An historical cohort of 425 patients from the cancer registry of the Province of Manitoba with squamous cell carcinoma of the oral cavity treated with surgery ±radiotherapy was examined. A Cox's proportional hazard model was used to examine the independent effect of surgical margins on five-year survival. Seventy-two percent of tumors involved the tongue and floor of mouth, and 43% of patients presented with Stage III and IV disease. The 5-year absolute and disease specific survivals were 62% and 74.5% respectively. Survival was related to age >65 years ($P = 0.0177$), T-Stage ($P = 0.0002$), and N-Stage ($P = 0.0465$). Patients with clear margins had a survival rate of 69% at 5 yrs (median survival >60 mos) compared to 58% with close (median survival >60 mos) and 38% with involved margins (median survival 31 mos, $P = .0000$). After controlling for significant prognostic factors, involved surgical margins increased the risk of death at 5 years by 90% (HR 1.9, 95% CI 1.2,2.9, $P = 0.0026$). The status of the surgical margin is an important predictor of outcome. The surgical margin, in contrast to the other prognostic indicators, is under the direct control of the surgeon.

Introduction

Microscopic tumor at, or close to the inked resection margin increases local recurrence by a factor of two or more in most series.[1–10] A negative impact on survival is not as clear, accepted by some[2,3,6,11,12] but not other investigators.[4,5,9,13,14] The status of the surgical margin has been associated with several factors that influence survival in

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oral cancer including the T-stage of the tumor,[6,8,15] N-stage,[6,15] and histopathological features including tumor thickness[4] and the pattern of invasion.[6,11,13] These observations indicate that the interactions between surgical margin status and treatment outcome in oral cancer are complex. This study was done to examine the independent effect of the status of the surgical margin on permanent pathologic section on local recurrence and survival.

Methods

An historical cohort of 707 patients with squamous cell carcinoma of the oral cavity from the cancer registry of the Province of Manitoba, Canada from January 1975 to present was examined. After excluding patients with incomplete records ($n = 34$), seen in consultation only or treated with palliative intent ($n = 69$), treated with radiotherapy as a single treatment modality ($n = 179$) there were 425 cases of biopsy proven and previously untreated squamous cell carcinoma of the oral cavity managed with surgery with or without adjunctive radiotherapy. Pathology reports were reviewed for the status of the resection margin. The presence of tumor at the inked resection margin was considered as positive. Tumor identified within 2 mm of the inked resection margin was recorded as close. Tumors were staged using the TNM classification.[16] Categorical data was evaluated using Pearson chi-square, with continuity correction when appropriate, or Fisher's exact test. A t-test or Mann–Whitney U-test was used for continuous variables. For survival analysis Kaplan–Meier curves[17] and log-rank test for comparing sub-groups was used. A multivariate Cox's proportional hazard model[18] was used to test the hypothesis of increased hazard or risk of death with close and involved margins after controlling for potentially confounding variables, such as age, tumor stage, etc. In addition, this model produced the adjusted hazard ratios (HR)[19] and the estimated adjusted probabilities of overall survival for each predictor in the model.

Results

The mean age of the cohort was 63.6 ± 12.6 years and 58.89% were males. Tobacco or alcohol use or a combination of both was documented in 80% of patients. One hundred and ninety-eight -second primary malignancies were identified in 145 patients, of which 61% were metachranous. The tongue was the primary site in 129 (30.4%) of patients, floor of mouth in 169 (39.8%), lower alveolus in 38 (8.9%), buccal mucosa in 33 (7.8%), upper alveolus in 23 (5.4%), and retromolar trigone in 33 (7.8%). One hundred and twenty-four patients had Stage I lesions, while 118, 68, and 105 patients had Stage II, III, and IV disease, respectively. Ten patients could not be staged. One hundred and seven patients (26%) had clinically positive nodes at the time of presentation.

Surgery was used as a single treatment modality in 298 (70.1%) patients and 127(29.9%) received adjuvant radiotherapy. Per-oral excision of the primary tumor was performed in 243 patients and 182 were managed with a composite resection. Mandible was resected in 175 patients, a marginal resection in 62 and segmental in 113. The clinically negative neck was treated electively in 120 patients (39.0%). Adjunctive radiotherapy was delivered by conventional fractionation, to a median dose of 5000 CGy (mode 5000 CGy). There were four deaths within 30 days of treatment completion. Minor morbidity was recorded in 23 patients treated with surgery (7.7%) and 42 (33.1%) treated with adjunctive radiotherapy ($P < 0.0001$). Major morbidity was observed in 8 (2.7%) of patients treated with surgery and in 10 (7.9%) of patients receiving radiotherapy ($P = 0.0313$).

Sixty-two patients (14.6%) had microscopic tumor identified at the inked resection margin, 68 (16.0%) patients had close (<2 mm), and 295 (69.4%) patients had clear (>2 mm margins). The relationships between the status of the surgical margins and clinical data is shown in Table 1. Involved margins were observed less frequently following excision of tongue tumors, however the observed differences did not achieve statistical significance ($P = 0.1239$). Involved margins were associated with both advanced T-stage ($P = 0.0033$) and the presence of clinically positive lymph nodes ($P = 0.0034$). The type of surgical resection did not influence the incidence of involved margins (Table 2). The use of intra-operative frozen section was not associated with either involved or clear margins. Adjunctive radiotherapy was used more frequently in patients with involved margins ($P = 0.0005$).

Recurrent disease, observed most frequently at the primary site and neck, was observed in 78 (43%) of patients treated with surgery and 46 (36%) of patients treated with adjunctive radiotherapy ($P = 0.24$). The relationships between margin status and the sites and incidence of recurrent disease and overall survival is shown in Table 3.

Table 1 Relationship of the status of the surgical margin to clinical data

Variable	Involved ($n = 62$)	Close ($n = 68$)	Clear ($n = 295$)
Age[a]			
>65 ($n = 199$)	33(16.6)	32(16.1)	134(67.3)
⩽65 ($n = 225$)	29(12.9)	36(16.0)	160(71.1)
Gender			
Male ($n = 250$)	41(16.4)	36(14.4)	173(69.2)
Female ($n = 175$)	21(12.0)	32(18.3)	122(69.7)
Site			
Floor of mouth ($n = 169$)	29(17.2)	26(15.4)	114(67.4)
Tongue ($n = 129$)	12(9.3)	17(13.2)	100(77.5)
Other ($n = 127$)	21(16.5)	25(19.7)	81(63.8)
T-status			
T1/2 ($n = 297$)	33(11.1)	46(15.5)	218(73.4)
T3/4 ($n = 119$)	27(22.7)	19(16.0)	73(61.3)
N-status			
N0 (308)	34(11.0)	48(15.6)	226(73.4)
N+ ($n = 107$)	25(23.4)	17(15.9)	65(60.7)

Numbers in parenthesis are percentages.
[a] The age of one patient was not recorded.

Patients with involved and close margins had a similar incidence of treatment failure, which was significantly higher than that observed in patients with clear margins. Failure at the primary site was more frequent in the presence of both involved and close margins. Margin status was not associated with failure in the neck or distant metastases. One hundred and ninety-eight deaths were documented, 73 attributed to oral cancer, 51 to second primaries, 44 from other conditions, and could not be accurately determined in 30. Sixty-two percent of the cohort survived five-years. Overall survival was significantly worse for patients with involved margins when compared to those with close or clear margins (Fig. 1).

The Cox's proportional hazard model is shown in Table 4. Age, T-stage, N-stage, and involved margins had a significant impact on five-year survival. After controlling for the confounding variables the presence of tumor at the inked resection margin increased the risk of death by 90% (HR 1.9). The presence of a close margin did not have a significant impact on survival.

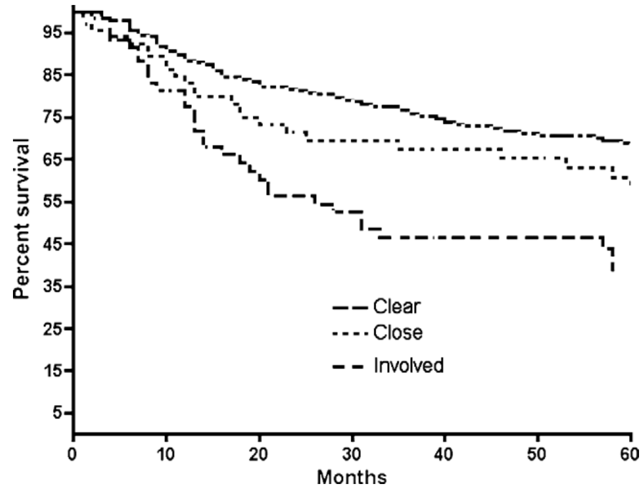

Figure 1 Kaplan–Meier survival curves showing five-year overall survival for patients with involved, close, and clear margins.

Table 2 Relationship of the status of the surgical margin to treatment parameters

Variable	Involved (n = 62)	Close (n = 68)	Clear (n = 295)
Resection			
Per-oral (n = 243)	31(12.8)	40(16.5)	172(70.7)
Composite (n = 182)	31(17.1)	28(15.3)	123(67.6)
Mandibulectomy			
Marginal (n = 62)	8(12.9)	14(22.6)	40(64.5)
Segmental (n = 113)	23(20.3)	15(13.3)	75(66.4)
None = (n = 250)	31(12.4)	39(15.6)	180(72)
Frozen section			
Yes (n = 225)	36(16.0)	31(13.8)	158(70.2)
No (n = 200)	26(13.0)	37(18.5)	137(68.5)
Adjunctive radiotherapy			
Surgery (n = 298)	31(10.4)	47(15.8)	220(73.8)
Surgery + radiotherapy (n = 127)	31(24.4)	21(16.5)	75(59.1)

Numbers in parenthesis are percentages.

Table 4 Cox's proportional hazard model predicting five-year overall survival

Variable	Hazard ratio	95% CI	P-value
Included in the model			
Involved versus clear/close margin	1.9	(1.2, 2.9)	0.0026
Age ⩾ 65 versus Age < 65	1.5	(1.1, 2.2)	0.0017
T-Status	1.4	(1.2, 1.6)	0.0002
N-Status	1.3	(1.0, 1.6)	0.0465
Excluded from the model			
Close versus clear margin			0.1027
Gender			0.3212
Treatment modality			0.6105
Stage			0.8805
Site			0.8379

Discussion

This historical cohort study of patients with squamous cell carcinoma of the oral cavity is relatively large. It is compa-

Table 3 Relationship of the status of the surgical margin to the incidence of recurrence, sites of initial recurrence, and five-year overall survival

	Involved (n = 62)	Close (n = 68)	Clear (n = 295)	All (n = 425)	P-value
Recurrence	25(40.3)	26(38.2)	73(24.7)	124(29.2)	P = 0.009
Site of recurrence					
Primary site	17(27.4)	16(23.5)	41(13.9)	74(17.4)	P = 0.005
Neck	14(22.6)	11(16.2)	37(12.5)	62(14.6)	P = 0.116
Distant Metastases	3(4.8)	5(7.4)	12(4.1)	20(4.7)	P = 0.207
Overall survival at five-years	38.7%	58.3%	68.4%	61.9%	P < 0.0001

Numbers in parenthesis are percentages.

rable in most respects, including the age and sex distribution, site distribution, etiologic factors, and incidence of second primaries, to most series of oral cancer.The incidence of involved margins (microscopic tumor at the inked resection margin) observed in this population based historical cohort was 14.6%. The reported incidence of involved margins following resection of head and neck cancers varies widely from 1 to 22%.[1–3,5–7,9,13,20] These studies with one exception[7] report single institutional experience and often include extra-oral sites.[1,3,5,7] Margins are more often positive in oral cancer than other sites in the head and neck.[5,15]

Tumor at the inked resection margin increased recurrence rates in this study consistent with previous observations.[1,2,6,7,9] An independent and significant impact on overall survival was demonstrated. Involved margins were associated with an increased tumor load, advanced T- and N-status, on presentation. The association of involved margins with factors that can independently influence outcome in oral cancer such as stage of disease[6,8,15] and adverse histopathological features such as tumor thickness[4] and unfavourable patterns of invasion[6,11,13] make the use of multivariate models necessary to assess the complex interactions of margin status and survival. Sutton and co-workers,[6] in a detailed analysis of the impact of margin status on outcome, included clinical findings as well as histopathology data including nodal involvement and extracapsular spread, pattern of invasion, perineural invasion and vascular permeation in their multivariate model. The relative risk of death for involved margins was 11.61 ($P = 0.0013$) and close margins 2.66 ($P = 0.02$). The only other factor with a significant impact on survival was positive lymph nodes (HR 2.15, $P = 0.063$). Other studies have failed to show an independent effect of positive or inadequate margins on survival with multivariate analysis.[5,13,14] Theses studies are not strictly comparable to the above series as they included significant numbers of patients with extra-oral tumors[5,14] previously treated patients[5] and a different definition for the ''positive margin''.[13,14]

Close margins (<2 mm) had a similar impact on the incidence and pattern of local recurrence as involved margins. Survival was not adversely effected by the close margin. Many investigators consider both close, and tumor at the inked resection margins together in their analysis of the impact of margin status on outcome.[8,11,21,22] When the impact of the close margin is reported separately the results suggest that the prognosis is better than observed in patients with tumor at the resection margin.[2,3,6,12] A major problem in assessing and comparing the results of studies evaluating margins is the fact that some series include patients with close margins and others do not. This problem is further compounded by the lack of a standard definition for the close margin. The most widely accepted definition of a close margin is tumor within 5 mm of the inked resection margin.[1–3,6,8,23] This is an arbitrary designation.[2,24] Others use <2 mm,[13,25] <3 mm,[12] within one high power field[9] or a variable definition related to the pattern of invasion at the tumor host interface.[10] In situ change and dysplasia have also been included.[1–3,6,8,21] This study did not address the impact of premalignant change at the margin. The balance of opinion would favor not including dysplasia in the definition.[23] The results of this study suggest that the outcome with tumor close to the resection margin should be reported separately from that observed with tumor at the inked resection margin as the prognosis differs. A standard definition for a close margin is necessary and this should be determined by a systematic evaluation of the effect of the width of resection on outcome.

Considering the significant impact on outcome precise definitions for the inadequate surgical margin are important clinically. Patients with assumed inadequate margins are considered for adjunctive radiotherapy. It is accepted that adjunctive radiotherapy in the setting of an inadequate may improve local-regional control[26–28] and possibly impact survival.[20,21] Adjunctive radiotherapy did not impact local and regional recurrence or survival in this study. It did however significantly increase morbidity.

The surgical margin is a prognostic determinant that is, at least in part, under the control of the surgeon as he or she determines the extent of resection in the individual patient. The clinical margin necessary to achieve an adequate histological margin has to take into consideration the fact that surgical specimens shrink, in the order of 40–50%[24] when fixed in formalin. Mucosal margins tend to receive the most attention, however most recurrences involve the deep resection margin. The importance of a three-dimensional resection is emphasized in the work of Ravasz et al.[8] Recurrence was not identified in patients with positive mucosal margins. Positive deep and multiple positive margins were associated with recurrence rates of 38% and 70%, respectively. The positive association of margin status with various tumor related factors observed in this and other studies indicates that negative margins are harder to achieve with large tumor loads, proximity to mandible and a posterior location in the oral cavity. The positive association of margins with unfavorable histopathology such as tumor invading deeply as nests and cords as opposed to a pushing front has prompted several investigators[6,14] to consider positive margins as an indicator of more aggressive disease. Patients with poor histopathological parameters with clear margins have a better outcome than patients with bad histology and positive margins.[8,22] The patient's expectations for a functional outcome also influence the extent of resection. There is no single definition for an adequate clinical resection margin. As defined by Yuen[25] the optimal resection margin should not compromise local control from an inadequate resection or cause unnecessary functional morbidity from too much resection. The use of intra-operative frozen section did not influence margin status in this study. Frozen section tends to emphasize mucosal and not the deep resection margin. In addition the common practice of assessing the patients resection margins,[23] does not identify the patient with a close margin.

In summary the status of the surgical resection is an important predictor of outcome, both local recurrence and overall survival in oral cancer. The presence of tumor at the resection margin, and close to the resection margin should be considered separately with respect to prognostic significance. Intra-operative assessment of resection margins needs to emphasize involvement and proximity of tumor to the deep resection margin. There is a need for a standard definition for the close margin in oral cancer based on a systematic evaluation of the impact of the width of the margin on outcome.

Conflict of interest statement

We the authors of this manuscript (A. Binahmed, R. Nason, A. Abdoh), have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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