MANDIBULAR INVASION IN ORAL SQUAMOUS CELL CARCINOMA

BY

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

MASTER OF SCIENCE

DEPARTMENT OF SURGERY
HEALTH SCIENCES CENTRE
UNIVERSITY OF MANITOBA
WINNIPEG, MANITOBA

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0-612-23202-6
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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

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ACKNOWLEDGEMENTS

I would like to express my sincere appreciation to my two supervisors, Dr. Richard Nason and Dr. Mark Cohen who inspired and guided me through this work.

The following are gratefully acknowledged for their assistance:

Dr. John Perry for his review of the pathologic slides.

Dr. William Gordon for his review of the panoramic radiographs.

Dr. Ahmed Abdoh for his assistance with the statistical analysis.

Mr. Larry Bluhm for his assistance with the gross pathology specimens.

Ms. Jeri Kostyra and the staff of the Manitoba Cancer Treatment and Research Foundation for their continued assistance throughout this study.

Ms. Emi Okamoto, my typist and computer assistant for the past three years.

and finally my wife, Mary Jane Thorne, for her love and support for the past five years.
Objective. To examine (1) the predictability of the orthopantomogram (OPG) in detecting mandibular bone invasion by oral squamous cell carcinoma (SCC), and (2) the independent effect of mandibular bone invasion on disease-free survival.

Study Design. A population based retrospective review of 107 patients with biopsy proven SCC of the floor of mouth, lower alveolus, and retromolar trigone, who required mandibular resection as part of their treatment was undertaken. Each patient received an OPG which was compared with the histologic findings of bone invasion. Bone invasion was categorized as none, focal (limited to cortex) and deep (cancellous extension). A multivariate Cox's proportional hazard model was then used to assess the independent effect of bone invasion on disease-free survival after controlling for the effects of potentially confounding variables in a stepwise fashion.

Results. The OPG identified 62% of patients with bone invasion by oral SCC. The OPG's lack of sensitivity (positivity in disease) however, allows for a relatively high incidence of false negative interpretations.

With the multivariate model, two variables, advanced clinical stage disease and deep bone invasion were found to be of prognostic relevance. Clinical stage of disease was determined to be a confounding variable of deep bone invasion, and after controlling for the effect of advanced clinical stage disease on disease-free survival, the independent effect of deep bone invasion failed to achieve statistical significance (p = 0.0845).
Conclusion. The OPG is a useful initial assessment of mandibular bone invasion by oral SCC, however, it lacks the sensitivity to detect the early stages of bone invasion. In this study, mandibular bone invasion was not shown to be prognostically significant for disease-free survival. Therefore, further investigations are unnecessary to determine if focal invasion of the mandible is present. It is more important to achieve with a marginal or segmental mandibular resection a clear resection margin. The OPG provides a good estimate of the gross extent of disease and an excellent general survey of the mandible to aid in surgical treatment planning.
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I. INTRODUCTION

Cancers of the oral cavity represent approximately 3% of all cancers diagnosed yearly in the United States\(^1\) and Canada.\(^2\) Each year there are 21,000 newly diagnosed cases in the United States and 2,100 in Canada.\(^1,2\) More than 90% of all oral cancers are squamous cell carcinomas (SCC).\(^1,3\) Some references report a higher incidence rate because of the inadvertent and inappropriate inclusion of pharyngeal, vermilion, and salivary gland cancers with oral cavity cancers.\(^3\)

The oral cavity is defined as the area between the vermilion border of the lips to the junction of the hard and soft palate superiorly, and to the line of the circumvallate papillae of the tongue inferiorly. It is divided into the following regions; lip, buccal mucosa, lower and upper alveolar ridges, retromolar trigone, floor of mouth, hard palate, and anterior two thirds of the tongue.\(^4\) Oral SCC adjacent to the mandible has the ability to invade bone by direct extension, necessitating mandibular resection.\(^5-7\) Mandibular bone invasion alters the staging and treatment of oral SCC.

Mandibular resection for oral carcinoma was originally described in 1906 by George Crile,\(^8\) whereby a primary carcinoma of the floor of mouth was removed en bloc with a segmental mandibular resection and associated submaxillary lymph node metastasis. The "composite" resection involved the removal of the intraoral primary in continuity with the regional lymph nodes (neck dissection) and intervening lymphatic channels (mandibulectomy). This was in keeping with cancer surgery in other areas of the body. In 1889, William Halstead increased the cure rate of breast cancer from 10% to 42.3% by performing an axillary lymph node dissection together with the radical mastectomy. In 1907, Ernest Miles developed the modern abdominoperineal resection for rectal carcinoma. In both surgeries, the primary lesion, intervening lymphatics, and regional lymph nodes were removed.\(^9\) Mandibular resection for oral
carcinoma was further supported by early anatomical studies by Eugene Polya, who
described the lymphatic drainage of the buccal mucosa to the neck through lymphatic
channels in the mandibular periosteum.\textsuperscript{10,11,12} Surgical treatment of oral carcinoma, as
described by Crile, was almost completely discarded at the turn of the century because
of the significant cosmetic and functional morbidity, high perioperative mortality, and
low cure rates. As a result, radiation therapy, with its ease of delivery and
minimization of anatomic deformity, became the accepted form of treatment for oral
carcinoma.\textsuperscript{13,14}

In the 1940's, there was a resurgence of surgical treatment for oral carcinoma.
It was recognized that radiation therapy was not curative for advanced lesions or those
invading bone.\textsuperscript{15,16} In addition, the advent of antibiotics and improvement in surgical
and anesthetic techniques "permitted the unhindered development of radical surgery
of the mouth, pharynx and neck."\textsuperscript{17} In 1949, Slaughter et al.\textsuperscript{16} reported their
experience with 73 patients requiring combined cervical node and mandibular
resections. As a general rule, the entire hemimandible was removed if bone was
invaded by tumor, or if the lesion was in the posterior oral cavity. A segmental (block)
resection sufficed for those lesions without bone invasion. The mandible was
considered a portion of the en bloc resection which included the intraoral primary,
regional lymph nodes, and intervening lymphatic channels of the mandibular
periosteum. Removal of the hemimandible during composite resection was carried out
to ensure complete extirpation of the tumor as the belief was that periosteal
lymphatics carried malignant cells away from the primary tumor to regional and distant
sites.

In 1951, Ward and Robben,\textsuperscript{13} described a "pull-through operation" for oral
lesions "so small" that there is no risk of periosteal involvement. This surgery was
performed for lateral tongue and base of tongue tumors, and was the first attempt at mandibular preserving surgery. Further interest in mandibular continuity sparing surgery grew from the functionally debilitating and poor aesthetic results associated with segmental mandibulectomy, in particular anterior segmental mandibulectomy, which was epitomized by the cartoon character "Andy Gump" of the 1930’s.18,19

From the 1940’s to the 1960’s, the oncologic principle of "en bloc" resection of the primary tumor, regional lymph nodes, and intervening lymphatic channels, was the surgical procedure of choice for many oral cavity cancers. At this time, researchers began to question the role of the mandibular periosteal lymphatics in cervical node metastasis.20 In 1964, a landmark study by Marchetta et al.5 showed that mandibular periosteal invasion does not occur without actual tumor abutment to bone, and that lymphatics draining the oral cavity into the neck are by alternate pathways other than through the mandibular periosteum. Carcinoma invasion of the mandible by direct extension rather than lymphatic spread was further confirmed by a follow-up study by these authors in 1971, and has been confirmed by others.6,7,21 These findings have encouraged consideration of mandibular continuity sparing surgery. For those patients with clinically uninvolved mandibles, a "pull-through" procedure, sagittal (lateral) resection, or marginal (occlusal rim) resection was recommended. Those patient with clinically involved mandibles underwent segmental (block) resection.14,16,22-24 Detecting mandibular bone invasion by oral carcinoma prior to definitive therapy continues as a challenge for the head and neck surgeon.

With the increased interest in mandibular sparing surgery influenced by Marchetta’s work, a number of studies have looked at the pattern of mandibular bone invasion by oral SCC. In 1966, Swearingen et al.25 coined the term "erosion" and "infiltration" to describe the radiographic appearance of carcinoma invasion of the
mandible. Other studies have confirmed that there are two different patterns of mandibular bone invasion seen with oral SCC. In erosive bone invasion, the tumor advances as a compact, broad front into bone, such that the tumor-bone interface is well defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the advancing tumor and receding cancellous bone. With infiltrative bone invasion, the tumor adopts a diffuse, irregular, infiltrating pattern, such that the tumor-bone interface is ill defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the infiltrating tumor and cancellous bone, often with islands of unresorbed bone left behind the advancing tumor.

The significance of these two defined patterns of bone invasion is that some authors have advocated marginal resection for erosive and early infiltrative lesions, and segmental mandibulectomy for infiltrative lesions extending beyond the mandibular cortex. Again, even with a better understanding of the pattern of bone invasion, confirmation of mandibular bone invasion prior to definitive therapy remains a challenge for the head and neck surgeon. This lies in the failure of radiographic assessment to identify early or small lesions restricted to the superficial alveolar bone or mandibular cortex. The alternative to classical composite resection has led authors to evaluate the radiographic assessment and the significance of mandibular bone invasion by tumor, along with the oncologic efficacy of marginal mandibulectomy.
II. LITERATURE REVIEW

II. A. EPIDEMIOLOGY

"The disease of our century is cancer." This statement was made by Dalitsch and Vazirami when they examined the increasing incidence of oral cancer in 1959.\(^3\) In 1900, cancer was the eighth most common cause of death in the United States after pneumonia and influenza, tuberculosis, diarrhea and enteritis, heart disease, cerebrovascular lesions, chronic nephritis, and accidents. Improved treatment of infectious diseases has now made cancer the second most common cause of death, while heart disease is ranked number one.\(^3\,^4\)

Oral cavity cancers account for 3% of all cancers diagnosed each year. This represents 21,000 (2,100) newly diagnosed cases in the United States (Canada). Slightly more than 6,000 Americans (600 Canadians) will die of oral cancer each year.\(^1\,^2\) India has the highest incidence of oral cancer in the world, which represents 50% of all cancers diagnosed there, and has been found to be directly related to the widespread habit of betel nut chewing.\(^2\,^3\) Oral cancer is the 6th (7th) most common cancer in males and the 12th (15th) most common cancer in females in the United States (Canada).\(^1\,^2\) Oral SCC represents 90% of all oral malignancies.\(^1\,^3\)

Oral SCC is stereotypically a disease of males in their 6th and 7th decade of life, who smoke and use alcohol. This impression, however, has not been stagnant over the past century.\(^3\,^5\) Currently, the reported male:female ratio for the disease ranges from 2:1 to 3:1.\(^1\,^3\) In 1935, the male:female ratio was 10:1; in 1960, 5:1; and in 1975, 3:1.\(^3\,^3\,^5\,^5\) When Chen et al.\(^3\,^5\) examined the changing trends of oral cancer in Connecticut, he recognized the increasing incidence of oral cancer in women and stated, "if this trend continues, the incidence of oral cancer in Connecticut women will
equal that of men by the mid-1990’s. In 1996, Oliver et al.\textsuperscript{37} reported their review of 92 cases of oral SCC from 1985 to 1992 and found a male:female ratio of 1.5:1.

Although the overall incidence rate for oral cancer (approximately 8 per 100,000) has remained constant through the 1940’s to the 1980’s, there has been a gradual decline in the number of male patients and an increase in the number of female patients, reflecting the change in the male:female ratio.\textsuperscript{1,2,35} Since 1960, with the first U.S. Surgeon General warning that cigarette smoking was the principle cause of lung cancer, follow by bans on tobacco advertising as well as cigarette tax increases, there appears to have been a decline in cigarette consumption for both men and women.\textsuperscript{38} In time, perhaps this may reflect a decrease in the incidence rates of oral cancer for both sexes.
II. B. ETIOLOGY

Sir Percival Pott in 1780 attributed scrotal skin cancer in chimney sweeps to chronic exposure to chimney soot. Soon after, the Danish Chimney Sweeps Guild made it mandatory for its members to bathe daily, resulting in a decrease in the incidence of this disease. The chemical carcinogen was identified as a polycyclic aromatic hydrocarbon (benzopyrene) which is present in fossil fuels and the combustion products of tobacco.\textsuperscript{38}

It is now believed that genetic mutation is the basis of neoplastic transformation and this has become widely accepted as the genetic theory or hypothesis. The experimental data and support for the genetic origins of cancer comes from the observation that agents (chemical, radiation, or viral), known to damage DNA (mutagens) are also found to be carcinogens. This was first realized when early researchers of x-radiation developed cancer from exposure. Years later, it was recognized that x-radiation is a potent mutagen.\textsuperscript{38,40}

Tobacco

Several etiologic factors are linked to oral SCC, but none so closely as that of tobacco. Typically 90\% of men and 60\% of women with oral carcinoma use tobacco.\textsuperscript{41-43} The incidence rate of oral carcinoma in smokers is six times greater when compared to non-smokers.\textsuperscript{44}

Tobacco use over time may cause progressive morphologic changes to the oral mucosa with eventual malignant transformation. The risk of malignant transformation is related to the amount of tobacco used and the duration smoked. The cessation of smoking leads to a progressively lower cancer risk.\textsuperscript{20,41} In support of this theory, Moore\textsuperscript{45} followed 203 smokers "cured" of their cancer of the upper aerodigestive tract
over a 7 year period and found that 40% of patients who persisted in smoking developed second cancers compared to 6% of patients who stopped smoking.

Endemic to India is the habit of chewing betel quid, consisting of betel nut and shell lime wrapped in betel leaf, to which tobacco may be added. The only carcinogenic agent to be identified in betel quid is tobacco and is reflected in people who chew betel quid without tobacco, failing to develop oral cancer.34,42,46

Alcohol

Alcohol alone was believed to be incapable of initiating oral cancer and was thought to act as a co-carcinogen (promoter) for other etiological factors.1,34 Recently, studies have shown epithelial dysplasia in the oral mucosa of non-smoking alcoholic patients, suggesting alcohol alone has direct carcinogenic effects.41 Indirectly, alcohol may induce carcinogenesis through nutritional deficiencies and liver dysfunction (decreased detoxifying capability).20

Typically, 75% to 80% of patients with oral carcinoma use or have used alcohol. The incidence rate of oral carcinoma in this group is six times greater compared to non-drinkers.20,41 It has been found that most heavy drinkers are also heavy smokers. Smokers who abstain from alcohol tend to smoke less compared to those who drink alcohol, and similarly for drinkers who do not smoke. The carcinogenic effects of alcohol and tobacco have been found to be synergistic rather than acting independently and being simply additive.47 The risk for a smoker to develop oral cancer is 5 times that of a non-smoker, and this risk increases to 15 times for a smoker who also uses alcohol.1,20

Boffetta et al.48 have shown the carcinogenic effects of tobacco and alcohol to act through direct contact and tend 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 the mouth and tongue. Similarly, the habit of chewing betel quid which is held in the buccal sulcus, is associated with carcinoma of the buccal mucosa, and the habit of reverse smoking where the lighted end of the cigarette is placed inside the mouth, is associated with carcinoma of the hard palate.

Radiation

Radiation (ultraviolet, x-rays, and nuclear fission) are recognized mutagens and carcinogens. This is reflected in the early researchers of x-radiation who developed skin cancer, miners of radioactive elements who developed lung cancer, and survivors of atomic bombs who developed leukemia. The past practice of using therapeutic doses of x-radiation for various benign conditions such as enlarged thymus and tonsils, sinusitis and acne, has resulted in a higher incidence of thyroid cancer in these patients years after treatment. These patients are theoretically at risk for development of primary oral carcinomas. The radiation associated with routine dental radiographs, however, is of such low dose that there has been no association with oral carcinomas.

Nutritional Deficiencies

Nutritional deficiencies have been associated with oral cavity carcinomas. Plummer-Vinson chronic iron deficiency syndrome (Paterson-Kelly Syndrome), commonly seen in northern Scandinavian women, is associated with an elevated risk for carcinoma of the upper aerodigestive tract. This condition has largely been eliminated with the public health measures of fortifying bread with iron. Epidemiological evidence shows that vitamin A, carotenoids (provitamin A), and
vitamin C may have a protective role against epithelial cancers. Therapy with retinoic acid (the form of vitamin A responsible for normal epithelial maturation) and beta-carotene (the major precursor of vitamin A) has been shown to reduce the severity of dysplasia in premalignant lesions.\textsuperscript{1,20}

**Immunosuppression**

Immunosuppression may play a role in the development of malignancies. Oral cavity carcinomas have been reported in patients receiving immunosuppressive drugs following organ transplantation. Patients with acquired immunodeficiency syndrome (AIDS) have a high incidence (20\%) of Kaposi’s sarcoma. Less common malignancies in AIDS patients are non-Hodgkin’s lymphoma and oral SCC. The immune system is thought to provide a surveillance function for neoplastic cells which display tumor specific antigens on their surface that are recognized by natural killer lymphocytes.\textsuperscript{1,41}

**Oncogenic Viruses**

Viruses have been implicated by association to play a possible role in the development of malignancies. The only virus, however, that is still considered to have a possible oncogenic role is the human papillomavirus which has been detected in oral dysplasia and carcinoma.\textsuperscript{20,41}

**Syphilis**

Syphilis has long been associated with the development of dorsal tongue carcinoma which was thought to be due to syphilitic glossitis in the tertiary stage. It is now understood that the carcinogenic agent was the arsenic compounds, which are
in part excreted in saliva, and were used to treat syphilis before the advent of modern antibiotics.30

Oncogenes and Tumor Suppressor Genes

Oncogenes and tumor suppressor genes are normal growth and differentiation genes which may become altered or activated by several agents (viral, chemical, and irradiation). Activation of oncogenes cause overexpression of the involved gene leading to the initiation and progression of a neoplasm. Tumor suppressor genes allow the development of neoplasia indirectly when they become mutated or inactivated. The ultimate actions of all carcinogens are thought to be through the manipulation of oncogenes and tumor suppressor genes.1,30

The most commonly identified mutated gene in oral SCC is the tumor suppressor gene p53 (located on chromosome 17) which plays a role in the regulation of cell proliferation. An altered (mutated) overexpression of the p53 protein is seen with oral SCC. Nitrosamines, a carcinogen in tobacco, can damage DNA leading to mutations that deregulate tumor suppressor genes or activate oncogenes causing neoplastic changes in the cell.30
II. C. PATHOLOGY

Carcinoma of the oral cavity is usually a relatively slow growing disease that follows a relentless course, eventually causing death to the patient by local tissue invasion, along with regional and distant metastasis. 62

Precancerous Lesions

Oral SCC may have its origin in white and red patches, while others will start de novo. A clinical white or red patch or plaque on the oral (and other) mucosa which cannot be rubbed off nor characterized clinically or histologically as any other disease is referred to as leukoplakia or erythroplakia. Leukoplakia and erythroplakia are strictly clinical terms which may represent precancer, whereas, epithelial dysplasia is a histologic term representing precancer. 1,51

Although leukoplakia is not associated with a histopathologic diagnosis, it is often considered to be a precancerous lesion. A precancerous lesion is a morphologically altered tissue where malignant change is more likely to occur than its normal counterpart. The clinical white color of leukoplakia results from a thickened keratin layer (hyperkeratosis) of the surface epithelium and/or a thickened spinous layer (acanthosis), which masks the underlying microvasculature (redness) of the connective tissue. In some cases leukoplakia may disappear spontaneously after removal of suspected etiologic factors, while others will slowly extend laterally and become thicker, appearing as a distinct white plaque (homogenous leukoplakia). Some progress, developing surface irregularities (nodular leukoplakia) or exophytic projections (verrucous leukoplakia). Some leukoplakias may exhibit dysplasia or invasive carcinoma with no change in clinical appearance, while other lesions eventually develop patches of redness (erythroplakia). This mixed pattern is referred to as
speckled leukoplakia or erythroleukoplakia. The red color of erythroplakia results from an epithelium that is immature and thinned (atrophic) and fails to produce keratin, allowing the underlying microvasculature to show through. Erythroplakia is particularly susceptible to malignant transformation.1,31,52

The etiologic factors of leukoplakia and erythroplakia are considered the same as those for carcinoma. Not surprisingly, 80% of leukoplakias are associated with smoking. Leukoplakia is the most common precancerous lesion of the oral cavity, representing 85% of such lesions, yet it is the least likely to exhibit epithelial dysplasia or early carcinoma. Erythroplakia is the rarest precancerous lesion of the oral cavity, and is more likely to exhibit epithelial dysplasia or early carcinoma. Histologic examination of 5-20% of leukoplakias reveal dysplasia or early carcinoma. This increases to 65% for speckled leukoplakia and 90% for erythroplakia.1,41,51

Not all oral cancers seem to be preceded by clinically evident precancerous lesions or histologically documented epithelial dysplasia. Some studies claim that up to 30% of oral SCC arise from pre-existing leukoplakia.53 Byers et al.54 examined SCC of the mandibular alveolus and found that 23% of the lesions had associated leukoplakia. Gujrathi et al.55 found 18% of oral tongue SCC was associated with leukoplakia in their study. If this were correct, then some cases of oral carcinoma would arise directly from clinically and histologically normal epithelium. Others have suggested that precancerous lesions always precede oral carcinoma but fail to be detected.20,51

**Site Predilection**

The most common sites of oral carcinoma are the lateral/ventral surface of the tongue and floor of the mouth accounting for 85% of oral carcinomas. This is
followed by the retromolar-anterior tonsillar pillar-soft palate complex, alveolar gingiva, buccal mucosa, dorsum of tongue, and hard palate. The site predilection of the "oral gutter" (lateral/ventral tongue and floor of mouth) for oral carcinoma has been explained by salivary "pooling" of carcinogens from alcohol and the combustion products of tobacco.  

**Early Oral Carcinoma**

The natural progression of a precancerous lesion is usually transformation from an in situ lesion to an invasive one. Early cases of oral carcinoma may often show clinical features as precancerous leukoplakia and erythroplakia. These early lesions may not have produced a mass or ulceration and for unknown reasons will progress in an exophytic or infiltrative fashion. The exophytic form tends to grow more superficially and metastasize later. It begins as an area of thickened epithelium which eventually heaps up along with ulceration. In more advanced cases, there is a progression toward deep infiltration. The infiltrative form is common in the tongue and begins as a firm mass covered by mucosa. There is deep infiltration with minimal surface elevation, and with more advanced cases, there is a progression towards exophytic manifestations along with ulceration.

**Second Primary Carcinomas**

A second primary carcinoma is distinct and geographically separate, such that it is not connected by neoplastic epithelial changes to the original primary lesion. There is a significant risk of a second primary carcinoma in patients with carcinoma of the upper aerodigestive tract. When a patient presents with an oropharyngeal carcinoma, there is a 15% chance of a synchronous second primary carcinoma.
a 6% chance per year, for at least 4 years after initial treatment, of a metachronous second primary carcinoma. The risk of a metachronous second primary carcinoma 4 years after initial treatment is reflective of the long term influences of carcinogenic agents such as tobacco.\textsuperscript{41,56}

Slaughter et al.\textsuperscript{57} in 1953 proposed the concept of "field cancerization" to explain the incidence of multiple primary carcinomas and their recurrence following complete resection. Studies have shown a recurrence rate of 35% at the primary site even though surgical margins were deemed to be negative.\textsuperscript{56,56} Slaughter postulated that oral carcinomas have a microscopic "multicentric origin" which grow independently and eventually coalesce to form a single macroscopic tumor. Carcinogens alter an area of epithelium such that there is a "field of preconditioned epithelium" with the potential to form multiple carcinomas synchronously or metachronously.\textsuperscript{58}

Local Invasion

As tumors grow in size they invade adjacent soft tissue and bone. A common symptom at this point is a painful ulcer that bleeds on contact. Tumor infiltration of the tongue may impair speech and deglutition with resultant weight loss. Further spread into the neck can lead to an orocutaneous fistula or erosion of a major blood vessel.\textsuperscript{52}

Mandibular Invasion

Oral carcinoma adjacent to the mandible has the ability to invade bone by direct contiguous extension.\textsuperscript{6,14,60} Slootweg and Muller,\textsuperscript{7,29} and O’Brien et al.\textsuperscript{31} found that the site of entry of carcinoma into the mandible was entirely dependent upon the location
of the tumor in relation to the mandible, the alveolar ridge for gingival carcinomas and the lingual cortical bone for floor of mouth carcinomas. O'Brien et al.\textsuperscript{31} found that the lateral and inferior aspects of the mandible were invaded by direct contiguous extension from metastatic fixed facial and submandibular lymph nodes. These findings are in contrast to McGregor and MacDonald,\textsuperscript{61,62} who found that the main route of entry for carcinoma entering mandibular bone was through the occlusal surface of the alveolar ridge and that the preferred pathway was through cortical defects. Their study, however, was restricted to edentulous mandibles whereby with atrophy over time the height of the alveolar ridge would be at the level of the floor of the mouth.

From the early studies of Polya\textsuperscript{10,11,12} it was believed that tumor reached mandibular bone by periosteal lymphatics which carried tumor cells from the oral primary to the cervical lymph nodes. This was the basis for aggressive resection of the mandible in the surgical treatment of oral carcinoma in the first half of this century.\textsuperscript{14} Marchetta et al.\textsuperscript{5,6} found that the mandibular periosteum was not involved unless there was direct contiguous extension of the tumor and concluded that the lymphatics draining the oral cavity use lymphatic channels other than the mandibular periosteum. This was confirmed by other studies\textsuperscript{7,21} and set the stage for consideration of mandibular sparing surgery in the treatment of oral carcinoma.

The periodontal ligament space has been suggested as a preferred pathway for carcinoma to invade the dentate mandible,\textsuperscript{63} but Totsuka et al.\textsuperscript{27} only observed this with the infiltrative pattern of invasion and not with the erosive pattern. It is now generally accepted that tumor invasion of the periodontal ligament space is seen only in association with direct contiguous extension of the tumor as part of the greater involvement of the mandible, and not as a preferential pathway for tumor entry into the mandible.\textsuperscript{7,29}
The inferior alveolar canal has been considered a preferential pathway for the spread of tumor in the mandible. In 1959, Panagopoulos examined 12 mandibles with carcinoma invasion and postulated that malignant cells cannot destroy the thick cortical bone, but find entry into the mandible via neurovascular channels of the periosteum. In 1970, Southam examined 15 edentulous mandibles resected for invasive SCC and found carcinoma spread along the inferior alveolar canal in 4 specimens. Totsuka et al. found that the infiltrative pattern of bone invasion can preferentially spread along the inferior alveolar canal however, the extent of this spread was "generally limited". This preferential spread was not observed with the erosive pattern of invasion. Like the periodontal ligament space, it is now generally accepted that tumor invasion of the inferior alveolar canal is seen only in association with direct contiguous extension of the tumor as part of the greater involvement of the mandible, and not as a preferential pathway for tumor spread.

Carcinoma invasion of bone can be thought of as occurring in 2 stages. The initial stage of bone destruction occurs by activated local host osteoclasts, which erode bone in front of the advancing tumor front. With the osteoclastic stimulation there is an associated osteoblastic stimulation, although to a lesser degree, on the opposite side of the bone trabeculae undergoing resorption. Tumors, including SCC, release osteolytic prostaglandins (PGE2 and PGF2α) referred to as osteolysins, which activate local host osteoclasts to resorb bone. It is also believed that the host inflammatory and immune cells associated with the tumor release osteolysins. The second stage occurs when the osteoclast response declines and the tumor cells continue the destructive process. The two stages may co-exist in different parts of the tumor. In irradiated mandibles the osteoblastic stimulation is not observed and is attributed to the effects of radiation.
Two different patterns of mandibular bone invasion are seen with oral SCC: "erosion" in which bone is eroded from an advancing tumor front and "infiltration" in which the tumor invades directly into cancellous bone.\textsuperscript{7,21,25-28} Brown and Browne,\textsuperscript{53} and Carter et al.\textsuperscript{60} suggested that the erosive and infiltrative patterns of mandibular bone invasion by oral SCC are not separate entities, but rather different phases of the same process. The erosive pattern progresses to a mixed pattern of erosion and infiltration, and finally into an infiltrative pattern of invasion as the tumor progresses through mandibular bone. Most studies support two distinct and separate patterns of bone invasion by tumor.\textsuperscript{7,21,25-28}

It is unknown what causes a tumor to adopt a particular pattern of bone invasion. Swearingen et al.\textsuperscript{25} correlated the pattern of invasion with cellular differentiation of the tumor. He found the erosive pattern to be associated with low grade tumors (well and moderately differentiated), and the infiltrative pattern to be associated with high grade tumors (poorly and undifferentiated). This correlation has not been supported by other studies, nor was the grade of histologic differentiation found to correlate with the presence or extent of tumor invasion.\textsuperscript{14,27,28,31}

Prognostic indicators of mandibular bone invasion are tumor location, size, and fixation to bone.\textsuperscript{14,28,68} The general expectation and finding is that larger tumors have a greater tendency to invade bone than smaller tumors, as well as those tumors that are in close proximity to bone as opposed to those that are not. Several authors\textsuperscript{14,29} caution that tumor proximity to bone rather than its size should be of primary consideration when assessing bone invasion. The small size of a tumor does not necessarily preclude the possibility of mandibular bone invasion. Gilbert et al.\textsuperscript{14} found the incidence of bone invasion to be 30% for those tumors clinically attached to the mandible, as opposed to 8% for those tumors that are unattached. The grade of
histologic differentiation and the presence of cervical node metastasis did not have a prognostic value for the presence of mandibular invasion by tumor.\textsuperscript{14,28}

Several authors have looked at the prognostic significance of mandibular invasion by tumor. Eicher et al.\textsuperscript{70} using univariate analysis found the presence of mandibular invasion to be prognostic for the presence of cervical node metastasis, however, mandibular invasion was not found to be significant by multivariate analysis. Soo et al.\textsuperscript{71} found mandibular invasion to be predictive of a lower survival rate with univariate analysis only. Multivariate analysis failed to confirm this conclusion. In a retrospective study of 1021 patients using multivariate analysis, Platz et al.\textsuperscript{72} found mandibular invasion to be of no prognostic relevance. Overholt et al.\textsuperscript{73} found the presence of mandibular invasion adversely affected survival with univariate analysis, such that the 5 year survival decreased from 85\% to 68\%. When multivariate analysis was performed however, mandibular invasion was only marginally significant (p < 0.1) in predicting a lower survival.

Regional Metastasis

At some stage during the disease process, the primary oral carcinoma will metastasize to regional lymph nodes. The involved lymph node with time will enlarge and eventually extracapsular extension will occur. The status of cervical lymph nodes is one of the most important prognostic indicators in determining outcome. The presence of regional lymph node metastasis further reduces survival by 30\% to 50\% compared to those patients without clinical evidence of metastasis.\textsuperscript{41,74}

On initial presentation, 40\% of patients will have clinically palpable cervical lymph nodes.\textsuperscript{38,75} The incidence of regional node metastasis increases correspondingly with T stage in the order of 20\%, 30\%, 50\%, and 70\%, with T1, T2, T3, and T4
tumors, respectively. Eicher et al. found that advanced T stage and decreased tumor differentiation were prognostic indicators of regional node metastasis by multivariate analysis. Nason et al. and Shah et al., in contrast, found no correlation between histologic differentiation and the presence of regional node metastasis. In addition, with increasing involvement of the number and level of lymph nodes, along with extracapsular spread, there is an adverse effect on survival. Extracapsular spread occurs in 75% of lymph nodes greater than 3 cm in diameter and further reduces survival by 50% compared to those patients with nodal involvement without extracapsular extension.

The incidence of false negatives (occult node metastasis) on clinical examination of the neck is 20% to 30%. Shah found that over 90% of patients with oral carcinoma and occult node metastasis had involvement limited to levels I (submandibular and submental triangle), II, and III (upper third and mid third jugular lymph nodes). Rarely were level IV (lower third jugular lymph nodes) and V (posterior triangle of the neck) involved. Nason et al. found that the untreated clinically uninvolved neck was the most frequent site of initial treatment failure, accounting for 60% of treatment failures. Approximately 25% of patients with clinically negative necks will eventually develop regional metastasis despite local control of their disease. This lends support for elective treatment of the clinically uninvolved neck. Nason et al. also found that 50% of the neck failures were contralateral to the primary tumor. This finding has been used as an argument against elective treatment of the neck. In comparison, development of regional metastasis in the electively treated (surgery or radiotherapy), clinically uninvolved neck occurs in only 5% of cases.

Vikram et al. compared failure in the neck following single and multimodality treatment. They found a recurrence rate of 36.5% for those patients who underwent
radical neck dissection for cervical lymph node involvement confined to one level. In comparison, the recurrence rate was 16% for those patients who underwent surgery and elective postoperative radiation therapy. The use of multimodality treatment has resulted in a decreased incidence of failure in the neck for patients with advanced disease.

**Distant Metastasis**

Uncontrolled or recurrent locoregional disease was the primary cause of death in most patients with oral carcinoma in the past. With improved locoregional control of disease, failure at distant sites has become a more significant cause of morbidity and mortality. Distant metastasis is usually preceded by locoregional recurrence and eventually occurs in 20% of patients with oral SCC. Only 4% of patients will develop distant metastasis without locoregional recurrence.\textsuperscript{82} It is thought that a metastatic cervical lymph node acts as a focus for spread to other regional lymph nodes and distant sites.\textsuperscript{76} Vikram et al.\textsuperscript{82} found that the incidence of distant metastasis was greater in those patients with cervical lymph node disease (25%) than those patients with uninvolved cervical nodes (4%). Two possible routes for dissemination are through regional lymphatics and the thoracic duct, and through tumor invaded blood vessels. It is the lymphatic system that is thought to be the most common route for systemic dissemination.\textsuperscript{83} Shingaki et al.\textsuperscript{83} found the presence of metastatic cervical lymph nodes to be the single most important indicator for the development of distant metastasis. The involvement of multiple nodal levels and the presence of extracapsular spread also has a detrimental effect on survival. The most common site of distant metastasis is the lung (56%), followed by bone (16%) involving primarily the vertebrae, ribs, and skull.\textsuperscript{83}
Eighty percent of distant metastasis occur within 2 years of treatment. Within 2 years of detection 90% of these patients are dead. Elective neck dissection has been advocated for those patients who are at high risk for developing regional metastasis, or may already have occult node micrometastasis. The rationale for this is a sequential progression from primary tumor to regional lymph nodes and then to distant sites. The advent of multimodality treatment of the diseased neck in the 1970's has lead to better locoregional control, and there has been a corresponding increase in the incidence of distant metastasis. This has prompted the investigation of systemic therapies such as adjuvant chemotherapy.
II. D. CLINICAL STAGING

The American Joint Committee for Cancer Staging and End Result Reporting (AJCC) was organized in 1959, for the purpose of developing a system of clinical staging of cancer. In 1954, the Union Internationale Contre le Cancer (UICC) was also working on a system of clinical staging of cancer. The AJCC and UICC joined together with the similar objective of developing an internationally accepted classification system and in 1988 agreed upon the TNM classification system (Table 1) of cancer that is now internationally accepted.4,54

The life history of cancer can be considered to go through three significant events; growth of the primary tumor (T), followed by spread to regional lymph nodes draining the area of the primary tumor (N), and finally distant metastases (M). The T, N, and M represent the significant events of the life history of the tumor and are the basis of the TNM classification system. There are 4 degrees of T, 3 degrees of N, and 2 degrees of M, resulting in 24 TNM categories. For ease of analysis the 24 TNM categories were condensed into 4 TNM stage groupings. The practice of assigning tumors to different stage groupings arose from the fact that early stage disease (localized tumors) had a better prognosis than advanced stage disease (metastasized tumors).55

The TNM staging system is a clinical staging system that represents the best estimate of the extent of disease as determined from clinical and radiographic examination. The purpose of staging is to give a pretherapeutic prognosis, determine treatment planning, and compare end results with other centers. There are some limitations to the TNM staging system. The extent of the disease is based upon clinical examination which relies on human judgement. For instance, clinical examination of the neck has a 30% false negative rate, while computerized
tomography and magnetic resonance imaging can further reduce the incidence of occult node metastasis to 20%. The presence of extracapsular spread and levels of nodal involvement, which adversely affect survival, are not included in the TNM staging system. Nor are tumor parameters such as histologic (differentiation), immunologic (surface antigens), and genetic (abnormal DNA), along with the nutritional and immunologic status of the patient, all of which are important prognostic indicators. Despite recognized problems with the TNM system, several studies have found the current TNM staging system to be prognostically significant for treatment outcome and useful for objective assessment of different treatment modalities.
<table>
<thead>
<tr>
<th><strong>Table 1. Definition of TNM classification system</strong></th>
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<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
</tr>
<tr>
<td><strong>TX</strong> - primary tumor cannot be assessed</td>
</tr>
<tr>
<td><strong>T0</strong> - no evidence of primary tumor</td>
</tr>
<tr>
<td><strong>Tis</strong> - carcinoma in situ</td>
</tr>
<tr>
<td><strong>T1</strong> - tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td><strong>T2</strong> - tumor more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T3</strong> - tumor more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T4</strong> - tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)</td>
</tr>
<tr>
<td><strong>Regional Lymph Nodes (N)</strong></td>
</tr>
<tr>
<td><strong>NX</strong> - regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td><strong>NO</strong> - no regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>N1</strong> - metastasis in a single, ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td><strong>N2a</strong> - metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N2b</strong> - metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N2c</strong> - metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>N3</strong> - metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>
**Distant Metastasis (M)**

- **MX**: presence of distant metastasis cannot be assessed
- **MO**: no distant metastasis
- **M1**: distant metastasis

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>NO</th>
<th>MO</th>
<th>T1</th>
<th>N1</th>
<th>MO</th>
<th>T2</th>
<th>N1</th>
<th>MO</th>
<th>T3</th>
<th>N1</th>
<th>MO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>-</td>
<td>NO</td>
<td>MO</td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td>Stage 1</td>
<td>-</td>
<td>NO</td>
<td>MO</td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td>Stage 2</td>
<td>-</td>
<td>NO</td>
<td>MO</td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
<td>T3</td>
<td>N1</td>
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</tr>
<tr>
<td>Stage 3</td>
<td>-</td>
<td>NO</td>
<td>MO</td>
<td>T1</td>
<td>N1</td>
<td>MO</td>
<td>T2</td>
<td>N1</td>
<td>MO</td>
<td>T3</td>
<td>N1</td>
<td>MO</td>
</tr>
<tr>
<td>Stage 4</td>
<td>-</td>
<td>NO,N1</td>
<td>MO</td>
<td>Any T</td>
<td>N2,N3</td>
<td>MO</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
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II. E. DIAGNOSIS

In evaluating a patient with an oral cavity tumor, the objective is to determine the type of tumor and the extent of disease. The diagnostic workup can be divided into history, physical examination, biopsy, and imaging studies.

History & Examination

Patients with oral carcinoma are often aware of an alteration in their mouth for a period of 4 to 8 months before seeking professional help. This may be explained by the fact that there is usually minimal pain in the early stages of growth. In addition the population group typically afflicted with this disease is of a lower socioeconomic level with a high consumption of alcohol and tobacco concurrent with oral neglect. Only one third of patients are diagnosed at early stage disease (stages I and II). Even though the diagnosis of oral carcinoma is relatively easy, it is often delayed, such that 50% of patients will have locally advanced disease, 40% will have palpable regional lymph node metastasis, and 15% will have a second primary carcinoma on initial presentation. The presentation of distant metastases on initial examination is uncommon.

Patients will often go to a dentist complaining of ill-fitting dentures, loose teeth, or pain associated with teeth or the mandible itself. The most common symptom of a patient with oral carcinoma is a persistent painful ulcer in the mouth, which may be associated with bleeding, slurred speech, dysphagia, and a neck mass. Neurologic disturbances in the mandibular branch of the trigeminal nerve is indicative of perineural invasion and advanced stage of disease.

Physical examination is essential for diagnosing and determining the extent of oral carcinoma with special attention to the high risk areas for developing carcinoma;
lateral/ventral surface of the tongue, floor of mouth, and retromolar-anterior tonsillar pillar-soft palate complex. Bimanual palpation is necessary to determine if there is deep invasion of the floor of mouth and tongue musculature. Tumor "fixation" to the mandible is significant for bone invasion. Detection of metastatic cervical lymph nodes is best done in conjunction with computerized tomography or magnetic resonance imaging as clinical examination alone fails to detect 30% of involved (occult) lymph nodes.18,76

Biopsy

The correct diagnosis of a lesion is essential before initiating treatment, as different tumors behave differently and thus require different treatment plans. Biopsy is mandatory to confirm the histologic diagnosis. There are several forms of biopsy; excisional, incisional, punch, core needle, and fine needle aspiration biopsy (FNAB). The majority of these techniques provide tissue for histologic diagnosis, while FNAB gives a specimen for cellular diagnosis (cellular atypia) using Papanicolaou (PAP) stain. FNAB is inexpensive, safe, quick to perform, and especially useful for evaluation of neck node masses. Definitive treatment, however, should not be performed on findings of FNAB alone, the diagnosis still needs to be followed and confirmed by histologic examination. In the past, FNAB did not gain widespread acceptance for fear of needle tract implantation, however, this has now been found to be unsubstantiated.74,86

Suspicious lesions or those that cover diffuse areas can be stained with toluidine blue, which has a preference for malignant tissue. Toluidine blue is an acidophilic, metachromatic nucleic acid stain, staining DNA and RNA, which dysplastic cells contain quantitatively more than normal tissue. In addition, with malignant tissue
there is loss of cellular cohesion resulting in intracellular canals which may facilitate retention of the dye. Epstein et al. found the use of toluidine blue to have a false negative rate of 8% and a false positive rate of 38% in identifying oral SCC. Areas of ulceration and inflammation also stain contributing to the high false positive rate. False positives, although more common, are less of a concern because these are followed up by biopsy for histologic confirmation. Due to the high false positive rate, toluidine blue is not recommended as a screening measure in the general population, but rather as a diagnostic aid for suspicious lesions.

Exfoliative cytology (cytologic smear) is of limited value in the diagnosis of oral carcinoma. The method uses cellular debris from the surface of a mucosal lesion and with PAP staining looks for cellular atypia. Even though it is inexpensive, quick, and painless, cytologic smears can have a false negative interpretation as high as 30% for biopsy proven oral SCC. Well differentiated tumors are more often associated with false negative smears.

Toluidine blue staining and exfoliative cytology are only aids to clinical detection of oral carcinomas. All positive responses by these tests must be followed up by biopsy and histologic diagnosis. Even negative responses must be viewed with clinical suspicion.

Imaging Studies

Radiologists are rarely the first to make the diagnosis of oral carcinoma. Oral carcinoma is almost always detected by clinical examination and very often by the patient's dentist when he/she presents with the complaint of a persistent sore, loose tooth, or an ill-fitting denture. The role of the radiologist is to determine the extent (stage) of disease, in order that the head and neck surgeon may properly formalize a
treatment plan. There is a 22% to 29% incidence of carcinoma invasion of mandibular bone on initial presentation.\textsuperscript{14,16,54,68-91} Weisman and Kimmelman\textsuperscript{69} found one third of all oral tumors that invade bone failed to show any clinical indication of mandibular involvement. The first assessment of carcinoma invasion of bone is usually by the clinician's physical examination. Studies have shown clinical examination to have a sensitivity (positivity in disease) of 30% to 60%, however, unpredictability lies in the high rate of false positive and false negative interpretations of 40% to 60%, and 10% to 30% respectively.\textsuperscript{14,58-91} Several imaging modalities have been used in conjunction with clinical examination to more accurately predict mandibular bone invasion by tumor. These have involved plain film radiographs (including panoramic tomography), computerized tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, and ultrasound (ultrasonography).

Plain film radiographs include routine mandibular views (posteroanterior, lateral, and oblique), periapical and occlusal dental films, and panoramic tomography (OPG). With the first commercially manufactured panoramic x-ray machine in 1961, panoramic tomography has generally replaced routine mandibular views in determining mandibular bone invasion by oral tumors.\textsuperscript{82,83} Panoramic tomography is more sensitive than routine mandibular views (conventional transmission radiography) in the detection of bone invasion because of the absence of overlapping images.\textsuperscript{84} The rotational technique of panoramic tomography allows for an excellent general survey of the mandible with easy clinical correlation. Superimposition of the cervical spine anteriorly, however, reduces the quality of the radiograph in the midline making accurate diagnosis of symphyseal lesions difficult.\textsuperscript{67,95,96} This can be overcome by taking additional radiographs such as occlusal dental films which are superior for the symphyseal region. Other dental films are not always easily obtainable. Positioning the
film often stimulates the patient's gag reflex or pain in association with the tumor. Panoramic tomography is easy to obtain and causes no discomfort to the patient.

The ability of panoramic tomography to detect mandibular bone invasion by oral carcinoma has been examined by several studies which report a sensitivity of 60% to 64%. There must be as much as 30% to 50% of mineral loss in bone before there are any visible defects on panoramic tomography, as a result the radiograph underpredicts the extent of tumor spread. Panoramic tomography's relative lack of sensitivity, that is the inability to detect the early stages of mandibular bone invasion, allows for a high incidence of false negative interpretations, which have been reported to range from 14% to 46%. O'Brien et al. examined the sensitivity of panoramic tomography in detecting mandibular bone invasion when the tumor was restricted to the periosteum and superficial cortex and found a false negative rate of 44%, confirming the radiograph's limitation to detect early lesions involving bone. With the radiograph's lack of sensitivity, there is the advantage of a correspondingly low incidence of false positive interpretations, which have been reported in the range of 0% to 8%. The dentate mandible, along with periodontal disease, osteomyelitis, and osteoradionecrosis, all of which have similar radiographic presentation, and the inherent limitations of panoramic tomography (cervical spine superimposition) result in false positive interpretations.

Unlike plain film radiographs, bone scintigraphy is extremely sensitive in detecting bone invasion with studies reporting 80% to 89% sensitivity. As a result of not being specific for malignant disease, there is a high incidence of false positive interpretations of up to 53%. Correspondingly, a negative bone scintigraph can with almost certainty preclude mandibular bone invasion by tumor due to the low incidence of false negative interpretations of 0% to 4%. Bone scintigraphy uses
radioactive Technetium-99m labelled phosphate compounds. Changes in bone physiology with an increase in osteoblastic activity allow radioactive labelled phosphate compounds to be actively incorporated into new bone crystals, allowing for the detection of these sites by bone scintigraphy.\(^{32}\) Changes in bone metabolism of as little as 5% can be detected by bone scintigraphy and reflect the high degree of sensitivity of the technique.\(^{38}\) Bone scintigraphy is not specific for malignant disease, as periodontal disease, fractures, osteoradionecrosis, osteomyelitis, and even inflammation from a recent biopsy adjacent to the mandible can result in a false positive bone scintigraph in the absence of malignant bone invasion.\(^{59,91,95}\) Even tumors adjacent to the mandible can elicit an inflammatory response in the periosteum giving a false positive result.\(^{96}\) This periosteal inflammatory reaction adjacent to tumor, whether invading or abutting the mandible, is the reason bone scintigraphy overpredicts the extent of tumor spread.\(^{95}\)

The high incidence of false positive interpretations for malignant bone invasion precludes the bone scintigraph as a single investigative modality. It has been advocated that the combination of panoramic tomography and bone scintigraphy is the most reliable initial radiological screen for predicting mandibular bone invasion.\(^{32,100}\) A normal (negative) panoramic tomograph and bone scintigraph can almost with certainty preclude mandibular bone invasion. However, a positive bone scintigraph is nonspecific.\(^{14,90,95}\)

Computed tomography uses the same principles of physics as plain film radiographs, whereby differential tissue density attenuates x-rays producing an image, but detectors and a computer are used instead of films. The spatial resolution (the ability to separate objects that are close together) of plain film radiographs is greater than CT, however, the ability of the CT to differentiate soft tissues of similar density
unobscured by overlapping images outweighs this slight disadvantage.\textsuperscript{101} For this reason, CT accurately delineates the soft tissue extent of disease.\textsuperscript{81,86,101} The sensitivity of CT in the detection of cervical lymph node metastasis is reported to be 80% and this is comparable to the sensitivity of MRI.\textsuperscript{75} This compares favorably to the incidence of false negative clinical examinations of cervical lymph node metastasis of 30%.\textsuperscript{76}

The evaluation of mandibular bone invasion by CT can be difficult and disappointing. Brown et al.\textsuperscript{32} found CT to have a false negative rate of 28% when assessing carcinoma invasion of the mandible. This compares to another study which found CT to have a sensitivity of 62% in detecting bone invasion.\textsuperscript{67} Both studies found it difficult to differentiate between an irregular alveolar ridge and early bone invasion. The presence of teeth, along with amalgam restoration artifact, obscures accurate interpretation. Shaham\textsuperscript{36} also found CT to be "helpful in evaluating the primary tumor and the neck nodes, although its definite value in evaluation of the mandible was very limited".

Magnetic resonance imaging uses radio waves to create an image, as opposed to x-rays.\textsuperscript{101} Several authors found MRI to be less reliable than CT in the evaluation of mandibular bone invasion.\textsuperscript{32,67} Brown et al.\textsuperscript{32} compared different imaging modalities in predicting invasion of the mandible. After 5 of 35 cases, "the MRI was no longer used on account of its generally poor quality". Evaluation of cortical bone involvement is difficult with MRI, which presents as a void (black) due to the lack of signal (low number of mobile hydrogen protons) and is less sharply demonstrated on the image. The high intensity signal of marrow fat makes the MRI more useful in assessing the medullary spread of tumor.\textsuperscript{67,101} MRI does however, give superior soft tissue contrast with minimal amalgam restoration artifact when compared to CT.\textsuperscript{67,101,102}
Ultrasonography is of limited use in the detection of mandibular bone invasion by tumor because bone does not transmit sound. Ultrasonography has been found to be useful in the evaluation of cervical lymph nodes. On image, lymph nodes are sharply delineated because of the differential in the reflected sound waves compared to the surrounding fat. With a larger than normal lymph node, ultrasonography guided fine needle aspiration biopsy can be performed. This has been found to be the most accurate method in the evaluation of cervical lymph node metastasis.

With completion of clinical staging of disease, that is the assimilation of all information from clinical examination, imaging studies, and pathology; the patient should be presented at a head and neck conference or tumor board. Here the patient will be reviewed by the expertise of multiple disciplines; head and neck surgery, medical and radiation oncology, dentistry, pathology, radiology, speech therapy, nutrition, and social services. In this type of environment, the optimal and most comprehensive treatment plan can be formulated for this complex disease.
II. F. SELECTION OF THERAPY

A number of therapeutic modalities are available for the treatment of oral SCC, however, surgery and radiation, alone or in combination, are the primary therapeutic modalities.\textsuperscript{75, 80} Chemotherapy has no defined role in the treatment of oral cavity cancer. Patients with advanced disease and distant metastasis may be candidates for chemotherapy, however, studies have failed to show any change in survival.\textsuperscript{103} Interest in immunotherapy for cancer has developed from the recognition that human tumor cells have on their surface tumor specific or associated antigens, which elicit an immunologic response mainly from T-lymphocytes. The role of immunotherapy at this time is investigational.\textsuperscript{86, 104}

Treatment Considerations and Outcome

Precancerous lesions, such as patches of thin leukoplakia, are observed and do not require biopsy or treatment. Cessation of etiologic factors such as tobacco and alcohol, will help prevent progression to carcinoma.\textsuperscript{106} Isotretinoin (13-cis retinoic acid) has been shown to suppress premalignant lesions (epithelial dysplasia).\textsuperscript{1, 20} Changes in appearance suggestive of malignancy (erythroplakia) warrant biopsy. Localized areas may be excised, however, these lesions often have a diffuse presentation that precludes complete excision. A carbon dioxide laser can be used to excise or evaporate extensive lesions. Radiation therapy is not recommended for the treatment of leukoplakia. It may cause the disappearance of leukoplakia which will eventually reappear with time.\textsuperscript{105}

Early stage disease (T1 and T2 lesions) may be treated by surgery or irradiation with equal results.\textsuperscript{86} Surgery is preferred for small, well-defined, anterior lesions of the oral cavity. For these lesions, peroral excision requires less time than radiotherapy.
with fewer long-term sequelae. The resultant small surgical defect may be closed primarily, grafted with split thickness skin, or left open to heal by secondary intention. Radiotherapy is preferred for ill-defined or posterior lesions of the oral cavity that would make surgical exposure difficult. Functional disability with speech and deglutition is less with radiotherapy than with surgery, although this is not true with small tumors (T1 lesions). The disadvantage of radiotherapy is its ineffectiveness with larger tumors (T3 and T4 lesions) and the time demands (5-7 weeks) on the patient for completion of therapy. The long-term sequelae of radiotherapy are mucositis, xerostomia with associated rampant dental caries, trismus from fibrosis, and osteoradionecrosis. The required curative dose of 6500 to 7000 cGy is well above the level of 5000 cGy at which these sequelae begin to appear. The same complications are associated with brachytherapy (interstitial irradiation). Brachytherapy localizes treatment and is used to boost external beam irradiation from 5000 cGy to the curative dose of 6500 to 7000 cGy.\textsuperscript{20,41}

Marchetta et al.\textsuperscript{106} reviewed 70 patients treated with peroral excision for localized oral SCC measuring less than 2 cm in diameter. On 5 year follow up, 64% of the patients were disease free and 36% developed recurrent disease. Recurrent disease was treated with radical surgery and cured 28% of the treatment failures. This increased the percentage of disease free patients at 5 years from 64% to 75%. The study also examined 17 patients treated with peroral excision for localized oral SCC measuring 2 cm to 4.5 cm in diameter. The 5 year survival was similar between the two groups.

Advanced stage disease (T3 and T4 lesions) is best managed with a combined modality of surgery and irradiation.\textsuperscript{88} Postoperative radiotherapy improves locoregional control and survival with advanced stage disease. Vikram et al.\textsuperscript{99} compared single
(surgery) and combined (surgery and postoperative irradiation) modality treatment for advanced stage disease and found local control was better in the combined therapy group (39% compared to 2% recurrence rate). The overall 5 year survival for oral SCC has improved from 25%\textsuperscript{107} with radiotherapy alone to 50%\textsuperscript{78} with combined therapy. These survival figures are comparable to other reported studies.\textsuperscript{30,75,86} The 5 year survival by stage, single modality treatment for early stage disease and combined modality treatment for advanced stage disease, is approximately 80%, 65%, 45%, and 25%, with stages I, II, III, and IV disease, respectively.\textsuperscript{20,30,75,78}

Surgical resection followed by postoperative irradiation is preferred because of better locoregional control and fewer treatment complications. The Radiation Therapy Oncology Group\textsuperscript{108} compared 5000 cGy preoperative to 6000 cGy postoperative irradiation in the combined modality treatment of advanced head and neck cancer. Locoregional control was better in the postoperative irradiation group (65% versus 48%). Preoperative irradiation is associated with difficult surgical dissection due to fibrosis and inflammation, ill-defined tumor margins, and wound healing complications such as tissue necrosis, infection, and fistula formation. These problems occur with the typical adjuvant radiotherapy dose of 5000 cGy. Postoperative irradiation has the advantage of addressing subclinical residual tumor and positive margins without the wound healing complications.\textsuperscript{20,41}

Reconstruction

Reconstruction of the oral cavity after ablative cancer surgery, in particular advanced stage disease, remains a challenge for the head and neck surgeon. Defects of the oral cavity require reconstruction to restore function and esthetics. Historically, soft tissue defects were left open to heal by granulation or adjacent tissues were
mobilized for approximation and primary closure. This often resulted in unsatisfactory function and esthetics as exemplified by the cartoon character Andy Gump.

The introduction of two pedicled regional tissue flaps, the forehead flap and deltopectoral flap in the 1960's, were a tremendous contribution towards reconstruction and set the trend towards immediate reconstruction following tumor extirpation, as opposed to prior complicated staged reconstruction with "tube flaps". These flaps, as with other pedicled regional flaps such as the pectoralis major myocutaneous flap, were the first to provide adequate soft tissue for immediate reconstruction. In the 1980's, a new dimension to reconstruction was added with advances in microvascular surgical techniques that allowed surgeons to transfer composite sections of tissue to distant sites in a single operative procedure. The first was the vascularized radial forearm free flap, developed in China in 1978. This flap was reliable, thin, hairless, and pliable, making it attractive for reconstruction of head and neck defects. Other vascularized free flaps have been developed, including composite free flaps allowing immediate vascularized bone grafts.

Management of the Mandible

The increased understanding of the patterns of bone invasion by tumor (erosion versus infiltration), along with several imaging modalities to determine the extent of disease, have helped to reduce the uncertainties in planning mandibular resection (marginal versus segmental) in oral cavity cancer. Loss of mandibular continuity, results in functional disabilities with speech, mastication, and swallowing, all of which compound the severe psychological distress associated with facial disfigurement as a result of treatment. Our understanding of the spread of tumor from the oral cavity has
evolved over the past century. From the early studies of Polya\textsuperscript{10,11,12} in 1902, it was believed that tumor spread from the oral cavity via mandibular periosteal lymphatics to the cervical lymph nodes. This was the basis for routine segmental or hemimandibulectomy for those patients with suspected bone invasion and even those with tumors that were close to the mandible with intervening normal tissue.\textsuperscript{10} With the work by Marchetta et al.\textsuperscript{5} in 1964, it became apparent that there are no direct lymphatics through the mandibular periosteum from the oral cavity and that tumor spreads to bone by direct extension. This changed the aggressive approach of the past to surgery that maintains mandibular continuity in selected cases.\textsuperscript{111} Marginal mandibular resection is now advocated for those tumors that encroach the mandible but fail to provide a clear resection margin of 1-2 cm of normal tissue, and those with superficial invasion of the mandible.\textsuperscript{18,30,54,71,111} Several studies have examined the oncological efficacy of marginal and segmental mandibular resection and found local control of disease and survival to be similar for both treatments.\textsuperscript{22,71,72,112}

Marginal mandibular resection preserves mandibular continuity and avoids the functionally debilitating and poor aesthetic results associated with segmental mandibular resection. Barttelbort et al.\textsuperscript{113} determined that it was necessary to have at least a 1 cm thick segment of bone remain after marginal mandibulectomy to minimize the risk of postoperative fracture. Segmental mandibular resection results in deviation of the mandible towards the midline from contracture of the pterygoid muscles. This deviation, and resultant functional disability and poor aesthetics, is more severe with anterior mandibular defects. Lateral resection of the mandible produces only moderate disability with swallowing and speech which is often well tolerated by some patients negating the need for mandibular reconstruction. For these patients, adequate soft tissue reconstruction avoids "pulling" of the soft tissues that would
otherwise be approximated for primary closure and minimizes the disabilities associated with lateral mandibular resection.\textsuperscript{114} Proper occlusion of the remaining mandible is maintained by physiotherapy and an oral prosthesis.\textsuperscript{20,41} Anterior resection of the mandible however, produces considerable disability and deformity and should be reconstructed.

The goal of mandibular reconstruction is to restore as completely as possible function and cosmesis to preoperative levels. Just as soft tissue reconstruction of the oral cavity has evolved, so too has mandibular reconstruction. The first to investigate the possibility of bone regeneration was Ollier, a French surgeon who in 1860 published his experiments with transplantation of thin strips of bone (mostly tibia and femur) with the overlying periosteum.\textsuperscript{115} It was not until 1891, however, that the first description of a bone graft to a mandibular defect was published by Bardenheuer, who used an osteocutaneous pedicled flap from the forehead to fill a bone and soft tissue defect.\textsuperscript{115} Other pedicled regional flaps containing bone from the mandible and clavicle were developed, but it was not until the year 1900 when the first free bone grafts (primarily the tibia, femur, and rib) were employed to reconstruct the mandible.\textsuperscript{116}

World War I was a major stimulus for the development of grafting techniques in mandibular reconstruction owing to the significant number of soldiers with traumatic mandibular defects. Kazanjian et al.\textsuperscript{117} in 1918 reported his experience as a surgeon with the British Army in the treatment of gunshot wounds of the face accompanied by extensive loss of the mandible. The treatment involved three stages. First, early treatment of the wound was limited to the removal of dirt, fragments of bone and teeth, regular irrigation and dressings, in addition to life saving measures which would involve maintenance of the airway, hemostasis, nutrition, and the prevention of infection. During this time, the wound was left open for as long as several months
before reconstruction. The second stage involved restoration of mandibular contour and function with the use of an oral prosthesis. The prosthesis involved a metal arch with bands that would be cemented on the remaining mandibular teeth or a hinged appliance with a mandibular and maxillary denture that braced itself against the two arches. The prosthesis was also a framework for reconstruction of the soft tissues. The third stage involved restoration of the lower lip and chin by means of local sliding or rotational flaps from the cheeks and sides of the neck. If the patient had acceptable function and appearance with the oral prosthesis, bone grafting of the mandible would not be undertaken. If a bone graft was performed, it would likely have been a free bone graft from the tibia or rib. German surgeons during the war started using en bloc free corticocancellous grafts from the anterior iliac crest to reconstruct mandibular defects. This was reported in the German literature in 1916 and 1917, and soon afterwards surgeons of the allied armies started using this technique. At the Interallied Surgical Conference in Paris in 1920, Ivy reported a 76% success rate with delayed bone grafting for mandibular gunshot defects sustained by the American Expeditionary Forces.

In 1943, Kazanjian again reported his experience with mandibular reconstruction during World War II. The method of reconstruction was very similar to that which he reported in 1918. In 1943, however, Kazanjian had antibiotics to combat infection, soft tissue reconstruction was not limited to local facial flaps but also involved staged reconstruction using tubed cutaneous flaps from the anterior chest wall, and finally, the bone graft would likely have been from the anterior iliac crest rather than the tibia or rib. Another innovation during World War II was the use of a bone mill to provide corticocancellous bone chips from the iliac crest to reconstruct a mandibular defect. Fixation of the bone ends was achieved by an oral
prosthesis or by the recently developed system of external skeletal pin fixation. The reported success rate of delayed bone grafting for mandibular defects sustained by American casualties in World War II was 90.7%. The sources of bone grafts were 836 from the ilium, 151 from the rib, and 23 from the tibia, for a total of 1010 mandibular bone grafts. In contrast, there were 123 bone grafting procedures amongst American casualties in WWI, with the iliac crest being utilized less than 6% of the time.

In 1949 and 1950, several surgeons reported their experience with "immediate" bone grafts of mandibular defects following tumor resection. Marino et al. reported their experience with immediate mandibular reconstruction using cancellous bone chips from the iliac crest. Cancellous bone chips were laid in the soft tissue bed of the former mandible and this was followed by primary closure of the soft tissues which acted like an envelope. The mandibular segments were held in place by an oral prosthesis and this was followed by 6 weeks of intermaxillary fixation. The authors also reported "extensive" use of antibiotics in order to have a successful outcome of the procedure. Edgerton et al. reported their use of en bloc corticocancellous bone grafts from the anterior iliac crest in the immediate reconstruction of mandibular defects. The bone graft was held in place by transosseous wires and was followed by a period of intermaxillary fixation. Other methods advocated for immediate mandibular reconstruction have involved bone plates (rigid internal skeletal fixation) with and without a bone graft bridging the mandibular defect, and titanium mesh trays (metal cribs) filled with cancellous bone from the ilium.

Immediate reconstruction of mandibular defects offered patients immediate mandibular function and facial aesthetics, however, the graft often failed because of salivary contamination and subsequent infection, or the prosthesis became exposed
due to inadequate soft tissue coverage.\textsuperscript{18,110,122,123} This caused many surgeons during the 1950's and 1960's to first perform adequate soft tissue reconstruction with stabilization of the bone ends for a period of 2 to 6 weeks, which would be followed by mandibular bone grafting via a submandibular approach to avoid salivary contamination. Stabilization was achieved by internal skeletal pin fixation (Kirschner wires), Steinman pins, or steel bars. These implants were considered "temporary spacers" because with time they tended to loosen and become exposed.\textsuperscript{110,116,124}

Immediate mandibular reconstruction became popular during the 1970's with the use of composite osteomyocutaneous pedicled regional tissue flaps, and even more so in the 1980's with the advent of revascularized composite osteomyocutaneous free flaps.\textsuperscript{18,85,109,110,122} The composite pedicled regional tissue flaps commonly utilized were the latissimus dorsi, trapezius, and pectoralis major, and with a periosteal blood supply carried portions of the scapula, clavicle, sternum, and rib to reconstruct the mandible.\textsuperscript{118} The most commonly used pedicled regional tissue flap, and often referred to as the "workhorse" in head and neck reconstruction, is the pectoralis major composite flap.\textsuperscript{118,125} The pectoralis major myocutaneous flap was introduced by Ariyan\textsuperscript{126} in 1979 as a means of soft tissue reconstruction in the head and neck after cancer resection. Compared to other pedicled regional flaps, the pectoralis major flap has a more favorable arc of rotation and is capable of providing various sizes and orientation of skin paddles making it very versatile.\textsuperscript{125} The pectoralis major myocutaneous flap has been used in conjunction with reconstruction plates in the restoration of mandibular defects, however, this has been plagued with a high incidence of plate exposure, in particular with anterior mandibular defects, with rates as high as 35\% to 50\%. Plate reconstruction alone is most effective with lateral mandibular defects where there is only a 5\% risk of exposure.\textsuperscript{127} Similar results are
achieved when a revascularized fasciocutaneous free flap is used in conjunction with a reconstruction plate.\textsuperscript{128} Surgeons have incorporated a portion of a rib or sternum with the pectoralis major flap for simultaneous reconstruction of bone and soft tissue defects, and have achieved better results than when a reconstruction plate was used without incorporating a bone graft in the flap.\textsuperscript{125,129}

Advances in microvascular surgical techniques have allowed surgeons to transfer composite tissue free flaps from distant sites for immediate mandibular reconstruction of bone and soft tissue defects in a single operation. A vascular free flap does not have the constraints of a pedicle, and with its own blood supply the graft is incorporated in the defect without depending on the vascularity of the recipient tissue bed. This has led to success rates approaching 96\% due to shorter healing time and greater resistance to infection and extrusion.\textsuperscript{116,122} The first vascularized free tissue transfer was a composite osteomyocutaneous radial forearm free flap developed in China in 1978.\textsuperscript{109} Since then, other vascularized composite tissue free flaps have been developed to reconstruct mandibular defects using bone from the scapula, fibula, and iliac crest.\textsuperscript{100} Of these, the vascularized composite osteocutaneous fibular free flap has emerged as the most versatile for bone and soft tissue reconstruction of the mandible. The fibular free flap provides up to 22 cm in length of bicortical tubular bone for mandibular reconstruction. The bicortical nature of fibular bone allows for a high success rate of 92\% with osseointegrated implants.\textsuperscript{122,130}

Immediate microvascular free tissue transfer in mandibular reconstruction is not universally accepted. The technique increases operative time, requires specialized training and facilities, and has inherent complications with vascular patency (10\% incidence of thrombosis) requiring re-exploration of the graft with an overall failure rate of 5\%.\textsuperscript{129,131} Carlson and Marx\textsuperscript{131} maintain that microvascular composite grafts consist
of "overbulk ed soft tissue and straight, volume deficient, nonmandibular bone that is fractured in an attempt to gain arch form". They advocate an early (3 month) or intermediate (1 year) delayed bone reconstruction using allogenic freeze-dried ilium or a mandibular bone crib packed with cancellous cellular bone harvested from the ilium at the time of reconstruction. Adequate soft tissue reconstruction and stabilization of the mandible using reconstruction plates is performed at the time of tumor resection. If the patient is to undergo postoperative irradiation in excess of 5000 cGy, then hyperbaric oxygen treatment is given before and after bone grafting to optimize vascularity of the recipient tissue bed. They further advocate that delayed bone grafting respects the biology of squamous cell carcinoma in that 70% of recurrent disease will occur within 1 year of treatment, thus allowing for easier detection of recurrence and avoiding loss of the reconstruction.
III. STATEMENT OF HYPOTHESIS

The hypothesis of this study is two fold;

1) that the OPG is a useful imaging study in the initial assessment of mandibular bone invasion by oral SCC, and

2) mandibular bone invasion by oral SCC, as an independent variable, is an adverse prognostic indicator of survival.
IV.

COMPARATIVE STUDY OF THE RADIOLOGIC & HISTOLOGIC FEATURES OF MANDIBULAR INVASION BY ORAL SQUAMOUS CELL CARCINOMA
INTRODUCTION

Two different patterns of mandibular bone invasion are seen with oral SCC: "erosion" in which bone is eroded from an advancing tumor front and "infiltration" in which the tumor invades directly into cancellous bone.\(^7\)\(^{21,25-26}\) The pattern of mandibular bone invasion by tumor can have an influence on surgical treatment planning, that is, marginal verses segmental mandibular resection.

Several authors have advocated that the erosive pattern of bone invasion,\(^7\)\(^{25-26}\) and early infiltrative lesions limited to the mandibular cortex,\(^7\)\(^{27,30}\) are amenable to mandibular preserving surgery. Due to its nature, erosive bone invasion produces a sharp, delineated margin between tumor and bone such that the actual extension of tumor into bone corresponds to the radiographic determination of bone involvement.\(^7\)\(^{27}\) The same does not hold true with the infiltrative pattern of bone invasion, which by its nature, produces a diffuse, ill defined margin between tumor and bone such that the actual extension of tumor into bone extends beyond the radiographic determination of bone involvement. Segmental mandibular resection is therefore recommended with infiltrative lesions extending beyond the mandibular cortex.\(^7\)\(^{25-27}\)

The purpose of this study is to examine the predictability of the orthopantomogram (OPG) in detecting mandibular bone invasion by oral SCC, and to compare the radiologic and histologic features of mandibular bone invasion.
MATERIALS AND METHODS

This study consisted of 23 consecutive patients with histologically diagnosed SCC, who underwent mandibular resection as part of their treatment. Mandibular resection was deemed necessary either because of the clinical diagnosis of bone invasion or in order to achieve a clear resection margin. All patients were treated at the Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, Canada, from November 1991 to November 1996. Tumors were staged (clinical TNM stage groupings) according to the 1992 guidelines of the American Joint Committee on Cancer. Lesions were divided into three sites: floor of mouth, lower alveolus, and retromolar trigone. Those lesions which encompassed more than one site due to size, were classified by the center of the lesion. Patient characteristics along with tumor site, clinical TNM, grade, and type of surgical resection performed are shown in Table 1.

All patients received a preoperative OPG (Siemens Orthopantomograph 10) which was reviewed by a single radiologist blinded to the histologic findings. Radiographs exhibiting bone defects suspected from the tumor were classified into two types of bone invasion: erosion and infiltration. Erosive bone invasion was characterized by loss of cortical continuity with a U-shaped or scalloped excavation of cancellous bone. The resultant radiolucent defect has a well defined, smooth margin (Fig. 1). Infiltrative bone invasion was demonstrated by loss of cortical continuity where there is a gradual transition between bone destruction and uninvolved cancellous bone. The resultant radiolucent defect has an ill defined, irregular margin (Fig. 2).25,27,28

The resected tumors were fixed in 10% buffered formalin. Two to four cut slices of 5 microns thickness were made through the tumor at the center of bone
invasion as determined by gross inspection of the resected specimen. Cut slices of the specimen were then decalcified and processed for paraffin sectioning, followed by staining with hematoxylin and eosin. Histologic examination of the sections was performed by one oral pathologist without knowledge of the OPG classification. The histologic slides were examined for bone invasion and were classified into two types: erosion and infiltration. In erosive bone invasion, the tumor advances as a compact, broad front into bone, such that the tumor-bone interface is well defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the advancing tumor and receding cancellous bone (Fig. 3). With infiltrative bone invasion, the tumor adopts a diffuse, irregular, infiltrating pattern, such that the tumor-bone interface is ill defined. There is loss of cortical continuity with inflamed fibro-connective tissue between the infiltrating tumor and cancellous bone, often with islands of unresorbed bone left behind the advancing tumor (Fig. 4).7,21,27,29

The histologic findings of mandibular bone involvement were then compared with the radiographic findings, along with tumor location, stage, and grade.
RESULTS

The patients ranged in age from 42 to 85 years with a mean of 62.0 years. There were 16 males and 7 female patients for a ratio of 2.3:1. Of the 23 patients, 20 (87%) had the risk factors of tobacco and alcohol use. Pain was the most common presenting symptom in 17 patients (74%).

Three patients (13%) had stage I disease, 2 patients (9%) stage II disease, 6 patients (26%) stage III disease, and 12 patients (52%) stage IV disease on initial presentation (Table 2). The incidence of bone invasion was 33%, 50%, 33%, and 75%, with stages I, II, III, and IV disease respectively. The site of origin for the primary carcinomas in the 23 patients were 9 (39%) lesions involving the floor of mouth, 7 (30.5%) the retromolar trigone, and 7 (30.5%) the lower alveolus (Table 3). The incidence of bone invasion was 57%, 57% and 56%, with alveolar, retromolar, and floor of mouth lesions. Fourteen (61%) patients underwent segmental mandibular resection, of which 12 (86%) had advanced stage disease (stage III and IV lesions) and 2 (14%) had early stage disease (stage I and II lesions). Nine (39%) patients underwent marginal mandibular resection, of which 3 (33%) had early stage disease and 6 (67%) had advanced stage disease. Of the 23 patients, 13 (57%) had histologic confirmation of mandibular bone invasion by oral SCC. Tumor differentiation was as follows: 2 (9%) poorly, 16 (70%) moderate, and 5 (21%) well differentiated (Table 4), and the incidence of mandibular bone invasion was 50%, 56%, and 60% respectively.

The radiographic and histologic findings of each individual patient is listed in Table 5 and a summary of the findings is presented in Table 6. In 18 of the 23 specimens (78%), the OPG correctly correlated with the histologic findings of either infiltration or no bone involvement. The OPG did not identify any of the 4 erosive lesions. Of the 13 specimens with histologic confirmation of mandibular bone invasion
by tumor, the OPG was positive in 8 for a sensitivity (positivity in disease) of 62%. All 8 specimens that the OPG identified were infiltrative lesions that extended beyond the mandibular cortex. There were no radiographic false positive interpretations in the study. The OPG failed to detect mandibular bone invasion by oral SCC in 5 of the 13 specimens, for a false negative rate of 38%. Histologically, these specimens were diagnosed as erosive (4) and infiltrative (1) bone invasion and all 5 specimens were found to be at the early stages of bone invasion and were limited to the mandibular cortex. Clinical examination alone, without the use of OPG radiographs, only identified 5 (38%) of the 13 patients with mandibular bone invasion.
DISCUSSION

The age of the patients was typical for the disease, while the male:female ratio of 2.3:1 differs from other reports of male:female ratios of 3 to 4:1.\textsuperscript{1,14,32} It may be explained by the increasing incidence of smoking among women.\textsuperscript{32} In 1959, Dalitsch and Vazirami\textsuperscript{33} recognized the increasing incidence of oral carcinoma in women and associated this with an increasing use of tobacco. They predicted that if the current trend continued the male:female ratio for oral carcinoma would approach 1:1.

The present study confirms along with other studies,\textsuperscript{7,29,32,99} the general belief and expectation that larger tumors have a greater tendency to invade bone than smaller tumors. This is clearly evident by directly comparing stage I and IV disease. There is a reversal of this trend when we examine stage II and III disease which may simply be a reflection of the number of cases in these two categories.

Brown et al.\textsuperscript{32} found a higher incidence of bone invasion by SCC of the alveolus (78\%) and retromolar (75\%) regions when compared to the floor of mouth (27\%). This study has shown a similar tendency towards mandibular bone invasion by those tumors which are in close proximity to bone, however the majority of floor of mouth tumors had bone invasion. This can be explained by the study design whereby a requirement of inclusion was mandibular resection as part of treatment, which was often the result of a large tumor. In this study, the floor of mouth tumors were at least T3 lesions.

No conclusions were drawn on the influence of histologic grade on tumor pattern (erosion versus infiltration) or extent of bone invasion. Previous studies\textsuperscript{14,27,29,31} also failed to show any correlation between the two. It has been suggested, however, that a dedifferentiated (poorly differentiated) tumor behaves in a more aggressive manner and is more likely to invade bone.\textsuperscript{25}
The ability of the OPG to detect mandibular bone invasion by oral SCC in this study compares favourably with other reported studies which range from 60% to 64%. The OPG’s lack of sensitivity, that is the inability to detect the early stages of bone invasion, allows for a high incidence of false negative interpretations. The reported values for false negative interpretations of the OPG range from 14% to 46%. The 5 specimens for which the OPG failed to detect a mandibular bone defect were histologically diagnosed as erosive (4) and infiltrative (1) bone invasion, however all 5 specimens were found to be at the early stages of bone invasion and were limited to the mandibular cortex. O’Brien et al. examined the sensitivity of the OPG in detecting mandibular bone invasion when the tumor was restricted to the periosteum and mandibular cortex and found a false negative rate of 44%. This confirms the OPG’s limitation in detecting early or small lesions involving bone.

The 8 specimens for which the OPG did detect a mandibular bone defect were histologically diagnosed as infiltrative bone invasion, and all were found to have tumor extending beyond the mandibular cortex. This is unlike the 5 lesions limited to the mandibular cortex that the OPG failed to detect. The sensitivity of the OPG in detecting infiltrative lesions alone was 89% (8 of 9 lesions were detected). Due to the sample size of this study, it is difficult to draw firm conclusions from this observation. Whether the OPG is more sensitive in the detection of infiltrative lesions or simply those that extend beyond the mandibular cortex is uncertain, since there were no erosive lesions that extended beyond the mandibular cortex.

Brown and Browne and Carter et al. suggested that the erosive and infiltrative patterns of mandibular bone invasion by SCC are not separate entities, but rather different phases of the same process. The erosive pattern progresses to a
mixed pattern of erosion and infiltration, and finally into an infiltrative pattern of invasion as the tumor progresses through mandibular bone. The erosive pattern occurs in the alveolar bone which has the ability to resorb in advance of the tumor. The mandibular basal bone is unable to resorb in the same fashion and the tumor adopts an infiltrative pattern of bone invasion. Brown and Browne\textsuperscript{63} found that approximately 25% of their cases exhibited a mixed pattern of bone invasion. The present study does not support this theory, which found two distinct patterns of bone invasion, erosion and infiltration, as previously described.\textsuperscript{7,21,25,29} Mixed patterns of invasion were not identified.

The OPG is a useful adjuvant to the clinical examination. On clinical examination alone, before assessment of the OPG, 5 (38%) of the 13 patients with mandibular bone invasion were correctly identified. The OPG further identified 3 patients with bone invasion that would otherwise have remained undiagnosed. One patient (number 18, Table 1) presented with swelling and discomfort of the retromolar region and only after assessment of the OPG was the underlying infiltrative lesion of the mandible discovered.

In conclusion, this study confirms that the OPG is a useful initial assessment of mandibular bone invasion by oral SCC. The OPG’s lack of sensitivity however, allows for a relatively high incidence of false negative interpretations. This is reflected in the OPG’s inability to detect the early stages of bone invasion where the tumor is limited to the mandibular cortex, which in this study were found to be mostly of the erosive pattern.
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Table 1: Clinical and histologic findings of 23 patients with oral squamous cell carcinoma.
Table 2. Clinical TNM stage grouping of disease and histologic findings of mandibular bone involvement

<table>
<thead>
<tr>
<th>Stage</th>
<th>Cases</th>
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<th>Erosion</th>
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<td>1</td>
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<tr>
<td>Stage 3</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Stage 4</td>
<td>12</td>
<td>8</td>
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<td>3</td>
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<tr>
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<td>23</td>
<td>9</td>
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<td>10</td>
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</tbody>
</table>

Table 3. Tumor location and histologic findings of mandibular bone involvement

<table>
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<th>Location</th>
<th>Cases</th>
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</thead>
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<tr>
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<tr>
<td>Retromolar</td>
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<td>3</td>
</tr>
<tr>
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<td>1</td>
<td>4</td>
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Table 4. Tumor grade and histologic findings of mandibular bone involvement

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<td>Moderate</td>
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<td>3</td>
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<td>2</td>
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</table>
Table 5. Individual patient radiologic and histologic findings of mandibular bone involvement

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<tr>
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<td>Nil</td>
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</tr>
<tr>
<td>3</td>
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<td>Infiltrative</td>
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<tr>
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<td>Nil</td>
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</tr>
<tr>
<td>8</td>
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<td>Erosive</td>
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<tr>
<td>9</td>
<td>Nil</td>
<td>Nil</td>
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</tr>
</tbody>
</table>

Nil = No bone involvement
Table 6. Summary of patient radiologic and histologic findings of mandibular bone involvement

<table>
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<th>Histology</th>
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<th></th>
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</thead>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
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</tbody>
</table>
FIGURE 1. OPG radiograph showing an erosive bone defect of the left mandibular retromolar region (arrow). The resorbed bone has a well-defined, smooth margin.
FIGURE 2. OPG radiograph showing an infiltrative bone defect on the left mandibular retromolar region (arrow). The resorbed bone has an ill-defined, regular margin.
FIGURE 3. Erosive bone invasion of the mandibular alveolus. Bone (B) is resorbed by an advancing tumor (T) front. Tumor-bone interface is well defined. Hematoxylin and eosin, original magnification x 1.
FIGURE 4. Infiltrative bone invasion of the mandibular symphysis. Bone (B) is resorbed by a diffuse, irregular infiltrating tumor (T). Tumor-bone interface is ill-defined. Hematoxylin and eosin, original magnification x 1.
V.

MANDIBULAR INVASION AND TREATMENT OUTCOME
IN ORAL SQUAMOUS CELL CARCINOMA
INTRODUCTION

Mandibular bone invasion alters the clinical staging of disease and thus the prognosis of oral SCC according to the TNM classification system. Studies have examined the prognostic indicators of mandibular invasion and found tumor location, size, and fixation to bone to be significant. There have only been a few studies, however, that have examined the prognostic relevance of mandibular invasion on survival. In a retrospective review of 1021 patients using multivariate analysis, Platz et al. found mandibular invasion to be of no prognostic relevance in overall survival. Soo et al. found mandibular invasion to be predictive of a lower survival rate with univariate analysis only. Multivariate analysis failed to confirm this conclusion. Overholt et al. also found the presence of mandibular invasion adversely affected survival with univariate analysis, however, multivariate analysis failed to confirm this. The present study is a retrospective review of oral SCC in the population (currently 1.1 million) of the Province of Manitoba, Canada, and was undertaken to examine the independent effect of mandibular bone invasion on disease-free survival.
MATERIALS AND METHODS

The charts of 360 patients with biopsy proven SCC of the floor of mouth, lower alveolus, and retromolar trigone, from January 1975 to November 1996, in the population based Manitoba Cancer Registry were reviewed. Two hundred and fifty-three patients with incorrect site coding, other pathology, insufficient clinical data, seen in consultation after treatment elsewhere, or who received radiotherapy to the primary as the only treatment modality were excluded. The remaining 107 patients underwent marginal or segmental mandibular resection as part of their treatment and provide the data for this study. The clinical records were analyzed for demographic factors, treatment modality, and treatment outcome. Patients were retrospectively staged from the clinical information recorded in the chart at the time of initial presentation according to the TNM classification system of the American Joint Committee on Cancer. Lesions were divided into three sites; floor of mouth, lower alveolus, and retromolar trigone. Those lesions which encompassed more than one site due to size were classified by the center of the lesion. Mandibular invasion by tumor was categorized as none, focal (invasion limited to the mandibular cortex), or deep (invasion with cancellous extension), according to the pathology report. If the pathology report did not supply sufficient detail as to the extent of bone invasion by tumor, the stored pathology slides were retrieved and reviewed by a single oral pathologist. To clarify presentation, the term "early clinical stage disease" denotes stages I and II lesions, and "advanced clinical stage disease" denotes stages III and IV lesions.

Categorical and continuous data were evaluated using the $\chi^2$ contingency table method and $t$ test, respectively. Disease-free survival was obtained according to the method of Kaplan and Meier. To calculate disease-free survival, patients dying
without cancer and those who were alive at the time of last follow-up, up to 5 years
were censored. A multivariate Cox’s proportional hazard model\textsuperscript{133} was used to assess
the independent effect of mandibular bone invasion on disease-free survival. In the
Cox’s proportional hazard model, the hazard ratio (or relative risk) is being modeled as
a function of both time and several covariables such as age, sex, tumor site, T stage,
and bone invasion. This time-to-event analysis estimates the probability that an event
(in this case death) will occur at different points in time, and also controls for the
effects of the potentially confounding variables such that the independent effect of
mandibular invasion can be examined. The hazard ratio (HR) calculated then is the
probability of dying for those patients with mandibular invasion compared to those
without mandibular invasion.
RESULTS

The patients ranged in age from 28 to 85 years with a mean of 62.2 years. There were 71 (66%) male and 36 (34%) female patients for a ratio of 2:1. The range of the follow-up period was from 0 months (death at time of treatment) to 60 months (completion of the study). In 87 patients whose social history was recorded, 88% used either alcohol or tobacco, or both. Pain was the most common presenting symptom in 76 patients (71%), followed by an intraoral ulcer in 62 patients (58%). Fifty-three second primary tumors were identified in 40 patients (37%), of which 36% were synchronous with the primary tumor. Sixty-four percent of second primary tumors occurred in the upper aerodigestive tract. Patient age and sex did not differ significantly between the three categories (none, focal, and deep) of mandibular invasion and were not found to be prognostically significant for disease-free survival.

Fourteen patients (13%) had stage I disease, 20 patients (18%) stage II disease, 18 patients (17%) stage III disease, and 51 patients (48%) stage IV disease on initial presentation. Four patients (4%) could not be staged accurately with the information provided (Table 1). The site of origin for the primary carcinomas were 53 (50%) lesions involving the floor of mouth, 31 (29%) the lower alveolus, and 23 (21%) the retromolar trigone (Table 2). Of the 107 patients, 48 (45%) had histologic confirmation of mandibular bone invasion by tumor. Tumor invasion was limited to the mandibular cortex (focal invasion) in 25 patients (23%) and cancellous extension (deep invasion) was found in 23 patients (22%). No bone involvement was recorded in 59 patients (55%).

Surgery was the single curative modality for 66 patients (62%), while 41 patients (38%) received a combined treatment modality of surgery and radiotherapy.
Concomitant treatment in the neck was performed in 85 patients (79%). Mandibular resection was part of the surgical treatment performed in all 107 patients of the study. Marginal mandibular resection was performed in 37 patients (35%), of which 1 (3%) had deep invasion and 36 (97%) had focal or no invasion by tumor. Segmental mandibular resection was performed in 70 patients (65%), of which 22 (31%) had deep invasion and 48 (69%) had focal or no invasion by tumor (Table 3). Primary closure was achieved in 22 patients (21%) after tumor extirpation. Soft tissue reconstruction was required in 73 patients (68%), of which concomitant mandibular restoration was performed with a reconstruction plate in 22 patients and a bone graft in 28 patients. The method of reconstruction was not recorded in the chart of 12 patients.

Locoregional recurrence occurred most frequently within 2 years of treatment (median 23.0 months). It was identified as the major cause of treatment failure and occurred in 32 (30%) of the 107 patients (of which 23 died of their disease). The most common site of recurrence was the primary in 14 patients (44%), followed by the neck in 9 patients (28%), combination of the primary and neck in 4 patients (13%), and distant metastasis in 4 patients (13%). The site of recurrence was not recorded in the chart of 1 patient. Mandibular invasion by tumor did not influence the pattern of recurrence.

Univariate models were used to analyze the following variables for their relationship with disease-free survival; patient sex (p > 0.6), age (p > 0.9), tumor site (p > 0.3), T stage (p < 0.05), N stage (p < 0.01), clinical stage (p < 0.025), mandibular invasion (p < 0.1), mandibular resection (p < 0.1), treatment modality (p > 0.2), neck treatment (p < 0.1), and the status of surgical margins (p > 0.1). The 5 year disease-free survival curves, with mandibular bone invasion as the only variable, were obtained.
according to the Kaplan-Meier method, and are shown in Figure 1. The two categories of mandibular invasion, none and focal, were not significantly different \( p > 0.6 \) in the prognosis of disease-free survival, and therefore were collapsed into one group for the purpose of multivariate analysis.

A multivariate Cox's proportional hazard model was used to assess the independent effect of mandibular bone invasion on disease-free survival after controlling for the effect of potentially confounding variables in a stepwise fashion. Table 4 shows the results of the multivariate analysis where deep bone invasion failed to achieve statistical significance \( p = 0.0845 \) after controlling for the effect of advanced clinical stage disease \( p < 0.0025 \) on disease-free survival. When adjusted for advanced clinical stage disease, patients with deep invasion have more than twice the risk of death with their disease during the 5 year follow-up as compared to patients with none or focal invasion \( (HR = 2.30; \ 95 \ C.I., \ 0.92-5.73, \ p = 0.0845) \). Survival curves generated based on this model are shown in Figure 2. For the reference group, early clinical stage disease with none or focal bone invasion, the 5 year survival probability was 97% and this decreased to 74% when advanced clinical stage disease (with none or focal bone involvement) was present. With the combination of advanced clinical stage disease and deep bone invasion the survival was further decreased to 50%. This decrease is due to the independent effect of deep bone invasion. The combination of early clinical stage disease and deep bone invasion (that was not detected clinically, but confirmed by pathology report only) did not significantly alter the 5 year survival probability (97% versus 93%).
DISCUSSION

The present study is a retrospective review of 107 patients with oral SCC and was undertaken to examine the independent effect of mandibular bone invasion on disease-free survival. This study differs from others in that it is from a population based tumor registry and in its full interpretation of a multivariate Cox's proportional hazard model. With this multivariate model eleven clinical and treatment variables were analyzed, and the two variables, advanced clinical stage disease and deep bone invasion were found to be of prognostic relevance. Furthermore, clinical stage of disease was determined to be a confounding variable of deep bone invasion, and after controlling for the effect of advanced clinical stage disease (p<0.0025) on disease-free survival, the independent effect of deep bone invasion failed to achieve statistical significance (p = 0.0845).

Clinical stage of disease may be more important in the prognosis of disease-free survival. However, in the context of this study it is only recognized as a confounding variable in the assessment of the independent effect of bone invasion. If there were no confounding variables, that is, each variable exerted an independent effect on disease-free survival, then the survival curves based on the Kaplan-Meier method would be identical to the survival curves based on Cox's proportional hazard model. Because of the effect of confounding variables, the survival curves generated by the Kaplan-Meier method will be inaccurate. Figure 1 shows the survival curves based on Kaplan-Meier method with bone invasion as the only variable and is unadjusted for clinical stage disease, and the 5 year survival probability for patients with deep bone invasion is 61%. In comparison, the survival curves based on Cox's proportional hazard model with the variable bone invasion adjusted for clinical stage disease shows the 5 year survival probability for patients with advanced clinical stage disease to
decrease from 74% to 50% when deep bone invasion is present. In the unadjusted model the 5 year survival probability of 61% lies between the survival probabilities of 74% and 50% of the adjusted model and is reflective of the confounding effect clinical stage disease has on bone invasion. The 24% decrease in 5 year survival probability is due to the independent effect of deep bone invasion in the presence of advanced clinical stage disease and is reflected in the hazard ratio (2.30) where patients with deep bone invasion have more than twice the risk of death during the 5 year follow-up as compared to those with none or focal invasion.

With the Cox’s proportional hazard model, the 5 year survival probability for patients with early clinical stage disease was not significantly altered (97% versus 93%) by the presence of deep bone invasion. This is because the clinical stage of disease is a confounding variable in the effect of deep bone invasion. In other words, the independent effect of deep bone invasion on disease-free survival was only seen in the presence of advanced clinical stage disease, and that effect only approached statistical significance in this study.

In conclusion, this study was fully able to interpret the Cox’s proportional hazard model which showed the independent effect of deep bone invasion on disease-free survival failed to achieve statistical significance after controlling for the effect of the confounding variable clinical stage of disease.
Table 1. Clinical TNM stage grouping of disease and histologic findings of mandibular bone involvement

<table>
<thead>
<tr>
<th>Stage</th>
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<th>Deep</th>
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<tbody>
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<td>0</td>
<td>12</td>
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<td>14</td>
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<tr>
<td>Total</td>
<td>107</td>
<td>23</td>
<td>25</td>
<td>59</td>
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X = cannot stage

Table 2. Tumor location and histologic findings of mandibular bone involvement

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<thead>
<tr>
<th>Location</th>
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<td>Floor</td>
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<tr>
<td>Alveolus</td>
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<td>19</td>
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<td>Retromolar</td>
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<td>9</td>
</tr>
<tr>
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<td>59</td>
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<td>25</td>
<td>59</td>
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</table>

Table 3. Mandibular resection and histologic findings of mandibular bone involvement
Table 4. Cox's proportional hazard model for the independent effect of bone invasion in mandibular cancer

<table>
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<th>P-value</th>
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<tr>
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<td></td>
</tr>
<tr>
<td>None (ref gp)*</td>
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<td>0.6703</td>
</tr>
<tr>
<td>Focal</td>
<td>0.75 (0.20, 2.84)</td>
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</tr>
<tr>
<td>Deep</td>
<td>2.52 (0.94, 6.70)</td>
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<td><strong>Adjusted Model:</strong></td>
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<tr>
<td>Bone Invasion</td>
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<td></td>
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<tr>
<td>None/Focal (ref gp)*</td>
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<td>0.0845</td>
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<tr>
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<td><strong>Clinical Stage</strong></td>
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</tr>
<tr>
<td>III/IV</td>
<td>9.99 (4.00, 24.91)</td>
<td></td>
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</tbody>
</table>

* reference group
Figure 1. Disease-free survival curves for bone invasion by Kaplan-Meier method (unadjusted for clinical stage disease).
Figure 2. Disease-free survival curves based on Cox’s proportional hazard model (adjusted for clinical stage disease).
VI. CONCLUSIONS

The present study is a population based retrospective review of 107 patients with biopsy proven SCC of the floor of mouth, lower alveolus, and retromolar trigone, who required mandibular resection as part of their treatment. It was undertaken to examine (1) the predictability of the OPG in detecting mandibular bone invasion by oral SCC to prove the hypothesis that the OPG is a useful imaging study in the initial assessment of mandibular invasion (23 of the 107 patients were suitable for this part of the study), and (2) the independent effect of mandibular bone invasion on disease-free survival to prove the hypothesis that mandibular invasion is an adverse prognostic indicator of survival.

The hypothesis that the OPG is a useful imaging study in the initial assessment of mandibular bone invasion by oral SCC was satisfied to be true by the first part of the study. The OPG identified 62% of patients with bone invasion by oral SCC. The remainder of the patients, for which the OPG failed to detect bone invasion, were all histologically diagnosed to be at the early stages of bone invasion where tumor was limited to the mandibular cortex (focal invasion). This demonstrates the OPG's lack of sensitivity in detecting early lesions and results in a relatively high incidence of false negative interpretations.

With the OPG's lack of sensitivity, bone invasion is not usually detected unless there is frank invasion of tumor into cancellous bone (deep invasion) and this was the finding of this study. The OPG provides a good estimate of the gross extent of disease and an excellent general survey of the mandible with easy clinical correlation to aid in surgical decision making such as marginal versus segmental resection. Marginal mandibular resection is now advocated for those tumors that encroach the mandible but fail to provide a clear resection margin of 1-2 cm, and for those tumors
with superficial invasion that permits 10 mm of mandibular height after resection.\textsuperscript{18,30,71,75,111}

The hypothesis that mandibular bone invasion by oral SCC, as an independent variable, is an adverse prognostic indicator of survival was not satisfied to be true by the second part of this study. Using the Cox's proportional hazard model, eleven clinical and treatment variables were analyzed, and two variables, advanced clinical stage disease and deep bone invasion were found to be of prognostic relevance. Clinical stage of disease was determined to be a confounding variable of deep bone invasion, and after controlling for the effect of advanced clinical stage disease on disease-free survival, the independent effect of deep bone invasion failed to achieve statistical significance.

In this study, mandibular bone invasion was not shown to be prognostically significant for disease-free survival, therefore further investigations beyond the OPG are unnecessary to determine if focal invasion of the mandible is present. It is more important to achieve with a marginal or segmental mandibular resection a clear resection margin at the time of tumor extirpation. Future studies to examine the impact of marginal and segmental mandibular resection on local recurrence and disease-free survival would be useful.
VII. REFERENCES


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120. Marino H, Turco NB, Craviotto M. Immediate reconstruction of the lower jaw following surgical excision of large tumors. Plast Reconstr Surg 1949; 4: 36-44.


