Oral Squamous Cell Carcinoma of the Maxilla

On the way to patient-specific care

Fons Joeri Bernard Slieker

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On the way to patient-specific care

PhD thesis, Utrecht University, the Netherlands

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Oral Squamous Cell Carcinoma of the Maxilla

On the way to patient-specific care

Oraal Plaveiselcelcarcinoom van de Maxilla

Onderweg naar patiënt-specifieke zorg

(Met een samenvatting in het Nederlands)

Proefschrift

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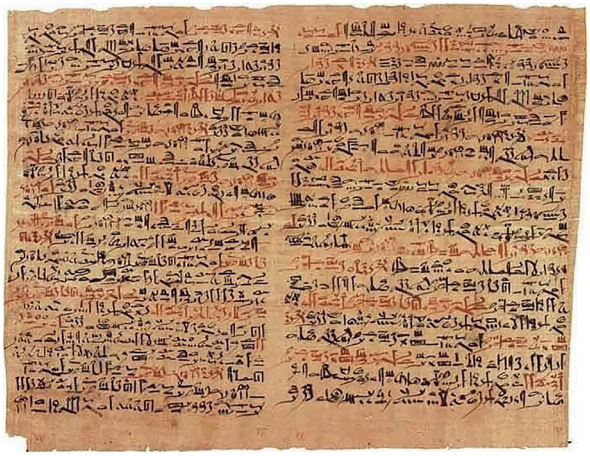
General introduction

Oral cancer in historical context

The word 'cancer' invokes many emotions. The term was credited to Hippocrates, who first described a tumorous lesion on the breast of one of his patients as καρκινος (karkinos) and καρκινωμα (karkinoma) in the 5th and 4th century BC. The non-cohesive growth pattern of a cancerous lesion reminded Hippocrates of the movements of a giant-crab (karkinos), infiltrating tissues with its claws [1]. Although the terms cancer and carcinoma are still being used today, they were not the first descriptions of cancerous lesions.

The first historical mention of oral cancer, "*bnwt*", was found in ancient Egyptian papyrus rolls called the Ebers papyrus and the Edwin Smith papyrus (Figure 1) [2].

Figure 1: An excerpt from the Ebers papyrus roll [2].



These rolls were dated to 1600 - 1550 BC, but likely contained copied information dating back to 3000 BC [1, 3-6]. The term "*bnwt*" was loosely translated as a cancerous eating ulcer of the gum. The ancient Egyptians utilised various forms of treatment for "*bnwt*", such as ointments made from animal tissues, vegetables, fruits and minerals, knives, cautery, hooks, drills, forceps, pincers, scales, spoons, saws, incense and arsenic paste [7]. One such example of a treatment was translated as follows:

"To drive out the "bnwt" that are in the teeth and to push the superficial flesh (gum): 1 bšbš-plant, 1 fruit of sycomore, 1 inst-plant, 1 honey, 1 terebinth resin (tree sap of the pistacia terbinthus), 1 water. (This) will be laid to rest during the night with the dew and then chewed" [8].

Travelling from ancient Egypt to ancient India, around 1000BC, another important medical treatise, the Sushruta Samhita, was composed. This was an encyclopaedic compendium on medicine and surgery, which possibly contained the first known effort to classify disease and injury based on signs and symptoms, including tumours. In the pathology chapter, various descriptions of different tumours were listed: "*arbuda*" referred to cancer, and "*ardudam*" referred to metastases. It also specified tumours according to specific locations in the mouth, for instance, "*arvuda*" referred to alveolar and palatal cancer [9-11]. Interestingly, the Sushruta

Samhita identified a risk factor for oral cancer that is still recognized today: chewing of betel quid, which is a mixture of areca nut, acacia catechu, and betel leaf [12, 13].

Classical – Medieval period

Hippocrates and his disciples first published a rational theory on the pathophysiology of cancer called the "*humoral theory*". This was the first time that cancerous disease was associated with natural causes and not with divine punishment [7]. The theory proposed that the body consisted of four humours, namely blood, yellow bile, black bile and phlegm. Any disturbance in the balance of these humours, caused by excess or lack of humours, could result in disease. Hippocrates associated cancer with effusion of these fluids in the soft tissue, lack of food and old age [14, 15].

Hippocrates was also aware of the communication between the oropharynx, nasopharynx, larynx and trachea. He therefore suggested deep examination of both nasal and oral cavities in cases of breathing disturbances, secretions and oral pathologies [16, 17]. Just like the ancient Egyptian and Indian doctors, Hippocrates proposed local surgical excision and cauterization, unless tumours were hidden, because those were deemed incurable [7].

After Hippocrates' death, medicine was established as a fully-fledged profession in ancient Greece [18-20]. Many developments by Greek, Roman and later Byzantine physicians have endured. Detailed descriptions of oral pathologies, like aphthae, gingivitis and glossitis have survived. Furthermore, detailed anatomical studies followed by new surgical techniques were developed for various kinds of oral cancer. Byzantine physicians even developed rudimentary anaesthetics for use during surgical procedures, based on extracts of analgesic and hypnotic herbs, such as *mandrake roots*, *papaverer somniferum L.*, *papaver rhoeas L.*, and *Hyoscyamus* [21, 22]. In time, monastic hospitals, called *Xenones*, were established in Constantinople. These precursors to modern hospitals were staffed by both male and female doctors and nurses. One could only work as a medical doctor after having attended the university of Constantinople under medical professors called '*iatrosofistes*', and having passed multiple examinations. Even members of the imperial Komnene family, like princess Anna Komnene and Emperor Manuele I Komnenos, worked as medical doctors in the *Xenones* [23-29]. It was not until after the fall of Constantinople in 1453, the subsequent exodus of Byzantine scholars to Florence and the start of the Renaissance, that scientific interest in medicine and oral cancer was reinvigorated in Western Europe.

Renaissance – Industrial period

Notably, after its introduction to Europe in the 16th century, tobacco was quickly identified as a primary cause for oral cancer. Whilst other countries, like France, Russia, Sweden and Switzerland outlawed tobacco altogether, King James I of England tried to discourage its production and consumption by imposing heavy tax laws [30]. Every country ultimately failed to halt tobacco consumption until centuries later in the 1960's, when the danger of smoking

tobacco was finally firmly recognized and wealthy countries started public health campaigns to discourage smoking [31].

Approximately 2000 years after the introduction of the humoral theory, a major scientific paradigm shift began when in the 1670's Antoni van Leeuwenhoek developed a microscope with very high magnification and the study of cells and micro-organisms was made possible. Because scientific progress was slow at first, this would only lead to significant breakthroughs in cancer research centuries later. Which brings us to the 19th century.

Figure 2: The introduction of ether by William Morton.

The first major breakthrough of the 19th century was the introduction of ether in 1846 by dentist William Morton (Figure 2). Morton performed the first procedure with ether to a college of surgeons in Boston. And although Morton tried to patent ether and reap the financial rewards for himself [32], the ethereal genie was already out of the bottle and it was not long before anaesthetics were widespread in use.

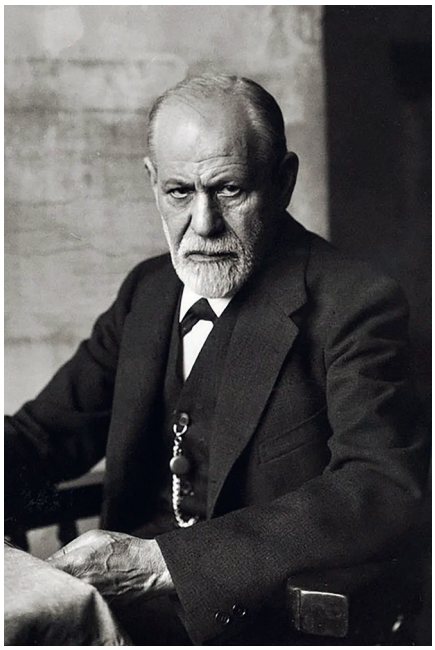
This was the key event that allowed surgeons time during procedures for more elaborate resections, whilst being able to control haemostasis [7]. Another major breakthrough was made in 1865 by Karl Thiersch and Wilhelm Waldeyer, who proved the origin of cancer from epithelial surfaces and subsequent invasion into the stroma. This was the beginning of the histological examination, determination of surgical margins, and further histological classification of malignant and benign tumours [33, 34].

Lastly, Henry Trentham Butlin, was the first head and neck surgeon to speculate that subclinical malignant disease of the neck might be cured by elective lymph node dissection [35-37].

Modern history

A historical patient of note with oral cancer involving the maxilla was Sigmund Freud, most famous for his development of psychoanalysis in the late 19th century (Figure 3). Freud was an avid smoker and habitual user of cocaine. By the time he was 67 years old in 1923, Freud had to undergo a partial maxillectomy procedure, because he was diagnosed with palatal cancer, most likely due to his excessive smoking of cigars and/or possibly affected by his cocaine habit [38]. The maxillectomy procedure was first described in 1827 by Lazar and performed successfully later that year by Joseph Gonsol [39]. Back then, these procedures were very dangerous, with high patient morbidity and mortality. The risk of infection and bleeding was high and if the patient lived, he often was severely disfigured with extensive facial scarring [39].

Figure 3: Sigmund Freud in 1926 [public domain].



The first maxillectomy of Sigmund Freud resulted in a massive haemorrhage and incomplete tumour resection. Many maxillectomies followed until eventually the entire maxilla of Freud was removed. His midfacial defect was treated with an elaborate prosthetic construction, which Freud called "the monster" [40]. Suffering from constant pain, unable to speak, chew or swallow, Freud never stopped smoking cigars. Sixteen years after his diagnosis, he passed away in 1939 [7, 41, 42].

After World War II, rapid advancements in medicine, surgical technique, imaging, genetics and computer technology changed the medical landscape dramatically [43]. This led to improvements in life-expectancy, disease burden and quality of life for patients with oral cancer involving the maxilla [39]. However, significant challenges remain.

Oral squamous cell carcinoma of the maxilla

Epidemiology

The incidence of oral cancer varies around the world by socio-economic conditions per country [44], with a global average of 4 cases per 100.000 [45]. In Europe, the incidence of oral and lip cancer is relatively high. In 2020, it varied between the lowest recorded incidence in Malta (4 cases per 100.000) and the highest in Hungary (11.4 cases per 100.000) (Figure 3) [46]. The incidence of oral cancer is increasing for both men and women (ratio 2:1) [45, 47]. Alcohol and tobacco consumption are still considered the most important risk factors associated with oral cancer in Europe [48], but their consumption has been relatively stable [49]. In 90% of oral cancer cases, it concerns squamous cell carcinoma [50, 51].

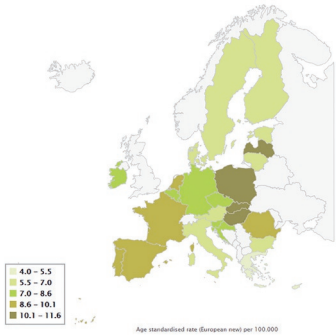


Figure 4: Incidence of oral cancer in 2020 in Europe from the European Cancer Information System at https://ecis.jrc.ec.europa.eu/ [accessed on 26 February 2021].

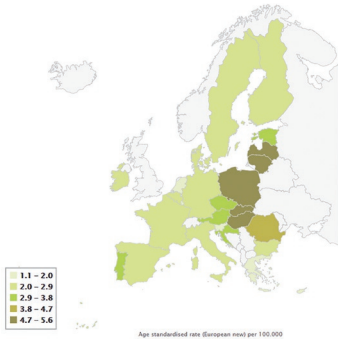


Figure 5: Mortality of oral cancer in 2020 in Europe from the European Cancer Information System at https://ecis.jrc.ec.europa.eu/ [accessed on 26 February 2021].

Between 2007 and 2011, each year an average number of 738 patients was diagnosed with oral squamous cell carcinoma in the Netherlands. Per anatomical sublocation these were: tongue 292 patients (40%), floor of mouth 205 patients (28%), buccal mucosa 122 patients (17%), lower alveolus and gingiva 76 patients (10%), upper alveolus and gingiva 28 patients (4%), and hard palate 15 patients (2%) [47]. Oral squamous cell carcinoma involving the maxilla (MSCC) can originate from the upper alveolus and gingiva and the hard palate. In other words, an average of 43 patients (6%) is diagnosed each year with MSCC in the Netherlands.

Throughout Europe mortality of oral cancer also varied considerably per country in 2020. The lowest was recorded in Luxembourg (mortality 1.1 per 100.000) and the highest in Hungary (mortality 5.6 per 100.000) (Figure 4) [46].

In the Netherlands and the rest of Europe, the survival rates of oral squamous cell carcinoma have been (marginally) increasing since 1989 [47, 52]. This can be attributed to earlier detection, better care access and improved treatments [52]. Because MSCC is a rare variety of oral cancer, exact results of treatment outcome are scarce.

Clinical presentation and evaluation of MSCC

Early diagnosis of MSCC is directly correlated with improved survival [53]. However, (pre) malignant lesions might present subtly and detection therefore usually requires skilled physicians and dentists [51]. Dentists are uniquely situated in the Netherlands to detect oral cancer early, because patients visit the dentist periodically for routine check-ups [54].

MSCC is often preceded by asymptomatic premalignant lesions, known as leucoplakia or erythroplakia. Leucoplakia is defined as a white patch or plaque that cannot be attributed to any other disease. Leucoplakia is at greater risk of malignant transformation if dysplasia is present (14.8-18.8% [55]); if the duration is long; if the size is greater than 2cm; and if the lesion is non-homogenous. Excision of leucoplakia should therefore be considered [51, 56, 57]. Erythroplakia is defined as a bright red velvety patch that cannot be attributed to any other disease. Risk of malignant transformation is high and excision is therefore recommended [51, 56, 57]. Oral lichen planus and oral submucous fibrosis have been associated with malignant transformation as well [56]. When a malignant lesion develops, patients might start to experience symptoms like the presence of a nonhealing ulcer, bleeding, loosening of teeth, ill-fitting dentures, facial numbness, pain and/or difficulty while swallowing, speech impediments and swelling in the neck [51, 56, 57]. In advanced stages, MSCC can invade the maxillary sinus, nasal cavity and the orbit. This might lead to symptoms of facial pain, cheek swelling, nasal obstruction, nasal discharge and epistaxis, ophthalmoplegia, diplopia and proptosis [58].

Systematic physical examination should be performed when patients present with these symptoms. Proper physical examination requires a good light source, protective gloves, tongue spatula and gauze. The physical examination should include the following components: extra-oral examination (inspection, bimanual lymph node palpation), lips (inspection, palpation), buccal mucosa (inspection, palpation), gingiva/alveolar ridge (inspection), tongue (inspection dorsal surface, ventral surface, and lateral borders, palpation), floor of mouth (inspection, palpation), hard palate (inspection), soft palate and oropharynx (inspection) [59]. If indicated, facial nerve examination should be included as well. In addition, the diagnostic workup includes clinical photography for future reference; tissue biopsy of the primary lesion; orthopantomogram for dental evaluation; magnetic resonance imaging (MRI), computed tomography (CT) and/or positron emission tomography (PET) scans to ascertain the involvement of soft and bony tissues, lymph nodes and distant metastasis; and ultrasound-guided fine needle aspiration cytology and/or sentinel node biopsy to assess lymph nodes involvement [51, 56, 57, 60].

The tumour-node-metastasis (TNM) staging system is subsequently used to stage and group the tumour (Table 1) [61, 62]. The tumour stage describes the volume and local invasiveness, with invasion of maxillary sinus, nasal cavity, orbit or pterygoid plates in advanced stages.

The node stage describes cervical lymph node involvement. The cervical lymph nodes are the first site of metastasis for MSCC. The cervical lymph nodes are grouped anatomically in 6 levels (Figure 6) [63].

Lymph node involvement usually follows a predictable step-wise pattern. Most frequently levels I – III are involved in MSCC [64]. The number of involved lymph nodes, lymph node size and extracapsular spread should also be registered. The metastasis stage describes the presence of distant metastasis. Distant metastasis is rare in MSCC, but if it occurs it usually involves the lungs, although it can also involve the bones and liver [65].

Tumour staging is essential to determine whether the goal of treatment is curative or palliative. Furthermore, it helps to determine which treatment modalities are best suited for specific patients. Lastly, it provides valuable insight in the prognosis of a patient [56, 57, 62].

Figure 6: Lymph node groups of the neck;

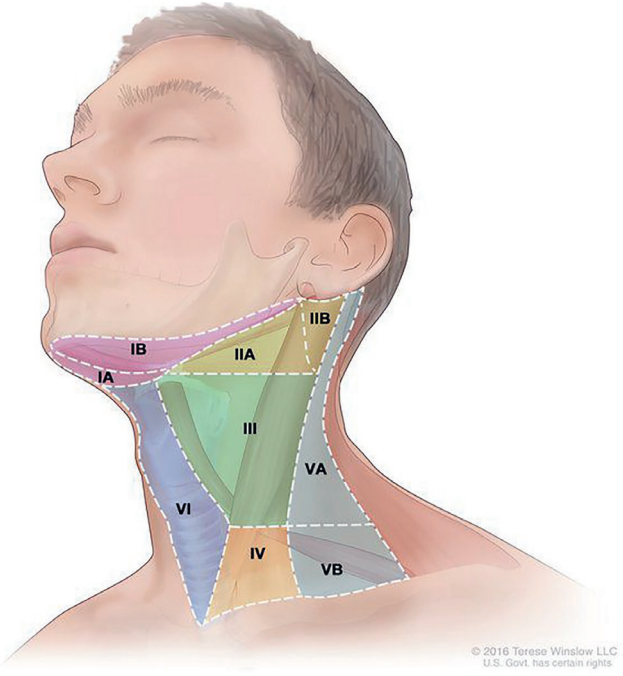


Table 1: TNM-staging of oral cavity cancer [61, 62]. Abbreviations: ENE, extranodal extension.

TNM-staging of oral cavity cancer	
	Primary tumour of the oral cavity
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness)
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm or tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm or any tumor >10 mm DOI
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery
	Regional metastasis
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; or more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative; or metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a	Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; or metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; or metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
	Distant metastasis
M0	No distant metastasis is evident
M1	Distant metastasis is evident

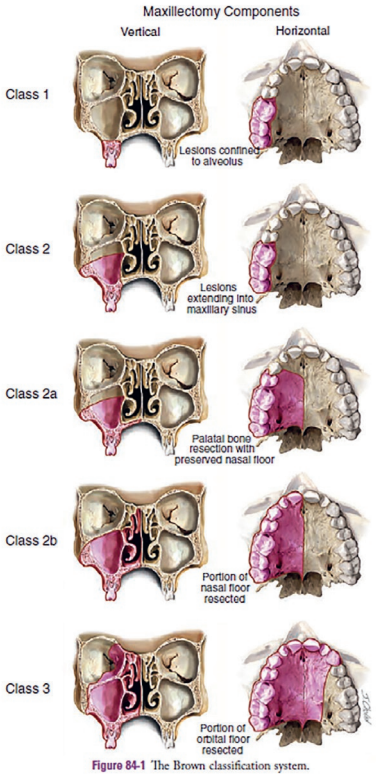
Treatment of MSCC

The preferred treatment for MSCC is surgery, so that radical resection of the tumour can be achieved [66, 67]. In the presence of bone invasion, resection of the tumour with "en bloc" resection of the affected bone is necessary to achieve adequate tumour free surgical margins. Therefore, reliable imaging techniques, like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), are commonly used during preoperative assessment.

Detecting bone invasion has been well-researched for the mandible, but not for the maxilla. That is why the first aim of this dissertation was to ascertain the value of CT and MRI in detecting bone invasion of the maxilla (chapter 1). This way, future preoperative assessment and surgical planning of MSCC might be improved.

Moreover, developments of promising imaging techniques like Cone Beam Computed Tomography (CBCT) are also recognized. CBCT imaging requires less time, produces lower radiation dosage and generates higher spatial resolution. Consequently, the second aim of this dissertation was to ascertain the potential value of CBCT in preoperative detection of bone invasion in MSCC (chapter 2).

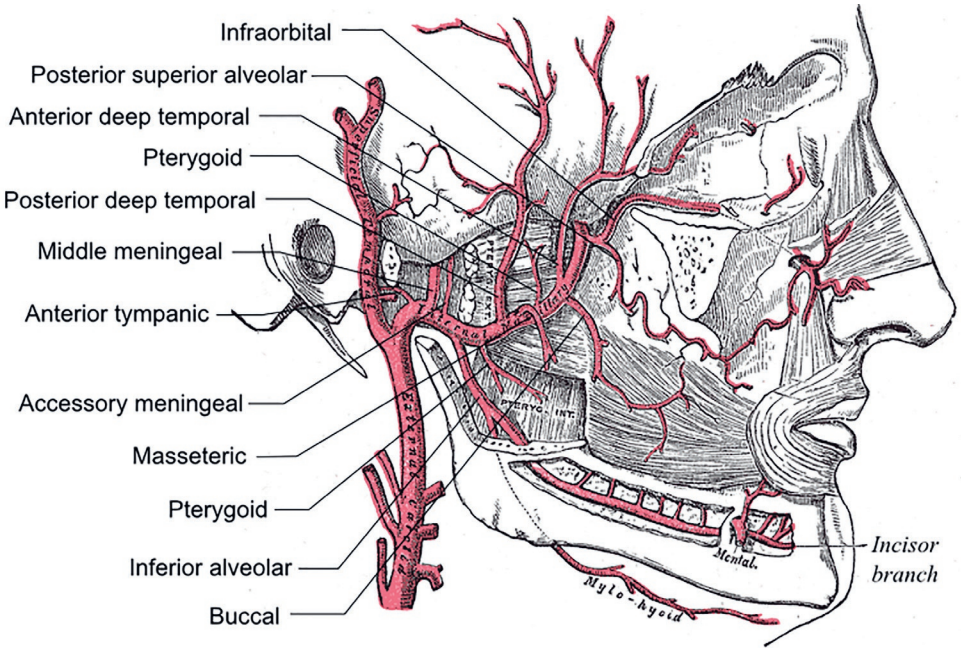
Figure 7: The Brown classification; this figure was published in the Atlas of Oral and Maxillofacial Surgery by Deepak Kademani and Paul Tiwana, chapter 84, page 871, ©by Saunders, an imprint of Elsevier, Inc. (2016) [with permission].



The Brown-classification provides a useful tool for planning the resection and reconstruction (Figure 7) [68]. The surgical approach and extent of the resection depend on the site and size of the tumour [69]. A transoral approach is suited for Brown class I and II. In case the tumour is located anteroinferior without ethmoidal involvement, an approach via midfacial degloving might be considered [70]. For Brown class III and more posterior lesions an extraoral approach via the Weber-Ferguson incision can be indicated [69]. An approach via a lower lip split and (para)median mandibulotomy can be appropriate if the tumour is localised in the posterior maxilla with extensive invasion of the pterygoid plates [71]. Lastly, the medial maxillectomy via a lateral rhinotomy incision might be preferable when the tumour is small and situated at the common wall separating the maxillary and nasal cavities [72].

The most common intraoperative complication is bleeding, because the maxilla and midface are well vascularized (Figure 8).

Figure 8: Internal maxillary artery and its branches. [this image is from the 20th U.S. edition of Gray's Anatomy of the Human Body, originally published in 1918 and therefore public domain.].



There are several sources of bleeding common during maxillectomy; mostly from sites such as the soft palate, hard palate mucosa, pterygoid plexus or skin flaps. Haemorrhage may be life-threatening in case the internal maxillary artery is transected or lacerated during osteotomy without exposing and ligating it beforehand; which is not always possible due to anatomical variation or tumour location [69, 73]. In that case, the maxillectomy should be completed expeditiously, after which pressure to the wound bed can be applied and then, with suction, the maxillary artery can be identified and clipped [73]. Other complications might include oronasal/oroantral communication, loss of vision due to optical nerve or corneal damage, or epiphora due to damage of the nasolacrimal system.

Surgical removal of maxilla tumours can be technically challenging because certain areas are difficult to access, and the visibility may be poor. Incomplete resection of large tumours and subsequent local recurrence account for a large proportion of patient mortality in MSCC. However, research about treatment outcomes and correlated risk factors, is still scarce. That is why the third aim of this dissertation was to obtain data, including predictive factors, on surgical treatment outcomes of MSCC (chapter 3).

Adjuvant treatment of MSCC

To reduce the risk of locoregional recurrence, patients are eligible for adjuvant treatment in certain cases. In case postoperative surgical margins were tumour positive and if re-excision was not possible, then adjuvant radiotherapy would be administered within 6 weeks of the

primary surgery. Also, patients with three or more risk factors for recurrence, such as close surgical margins, nerve invasion and pT3-T4 stage, would receive adjuvant radiotherapy.

More knowledge about previously unknown risk factors for local recurrence may improve the number of patients that may benefit from adjuvant treatment. Furthermore, identification of new risk factors may individualize follow-up strategies and aid in early detection of local recurrence, subsequently improving survival rates by timely salvage treatment. That is why the fourth aim of this dissertation was to have an in-depth look into risk of local recurrence, risk-reduction and salvage treatment outcomes (chapter 4).

Neck treatment

When multiple lymph node metastases are present or in case of extracapsular nodal spread or positive surgical margins in the neck, the neck should be treated with adjuvant radiotherapy. In case of positive surgical margins or extracapsular nodal spread cisplatin-based concomitant chemotherapy is added to radiotherapy, if patients are <70 years without contraindications for chemotherapy [60].

If during preoperative assessment cervical lymph nodes test positive for tumour involvement, neck dissection is indicated. As mentioned above, lymph node involvement usually follows a predictable step-wise pattern. Most frequently levels I – III are involved in MSCC (Figure 6) [64]. Therefore, a selective neck dissection with resection of levels I – III might be indicated in a clinically negative neck (cN0) or a single small metastasis (cN1). If more levels are involved, more extensive selective neck dissections, like (modified) radical neck dissection might be necessary (levels I – V, with/without resection of sternocleidomastoid muscle, accessory nerve and/or internal jugular vein) [74].

Unfortunately, when cervical lymph nodes test negative for tumour involvement during preoperative assessment, occult metastases might still occur in 24.1% of MSCC patients with T4 tumours, 14.3% of patients with T3 tumours and 13.6% of patients with T2 tumours. Furthermore, in 45.5% of these occult metastases the contralateral neck was markedly involved. Therefore, sentinel node biopsy or (bilateral) elective neck dissection in T2-T4 MSCC patients can be considered [75].

In case invasive procedures like sentinel node biopsy or neck dissection are contra-indicated or against the wishes of the patient, primary neck treatment with radiotherapy might be an alternative option.

Unfortunately, the impact and interaction of adjuvant treatment, neck treatment and multiple other risk factors on a patient's prognosis is difficult to assess. Reliable calculation of prognostic probabilities with prediction models may support both physicians and patients. There was no reliable prediction model specifically for MSCC available. Therefore, the fifth aim of this dissertation was to develop a new, accurate and reliable prediction model for MSCC (chapter 5).

Midfacial defect management

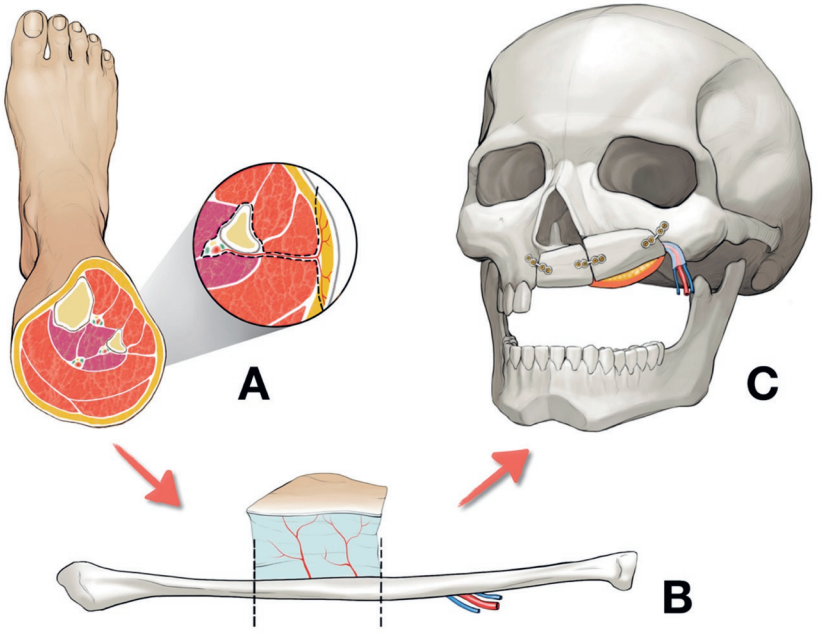
If the postoperative midfacial defect is not managed properly, the loss of orofacial function and cosmetic mutilation often leads to severe loss of life quality [76]. The midfacial defect can be managed by surgical reconstruction, either with pedicled flaps or vascularized free-flaps (Figure 9), or with the placement of an obturator prosthesis.

Although surgical reconstruction is the internationally accepted standard of midfacial defect reconstruction, they often have higher morbidity rates, donor site morbidity rates, prolonged surgical time and high costs [77]. Patients might therefore prefer the less invasive obturator prosthetics.

Historically, obturator prostheses were associated with discomfort, leakage, hygienic maintenance and regular modifications [77-79]. Recent developments however, like 3D-planning, implant-support and/or frame reconstruction have greatly diminished these problems [80]. Patients and surgeons often choose obturator prostheses, because they require less invasive surgical procedures, are generally cheaper, and it allows for easier physical examination of the resection margins during follow-up.

It has not been established which midfacial defect management strategy provides the best outcome for different midfacial defects. Exact data on usage of different types of midfacial defect management is not available. Thus, it seems that the choice is currently a matter of personal preference for both patient and surgeon. Accordingly, the sixth aim of this dissertation was to acquire an overview of midfacial defect management strategies in clinical practice across different centres in the Netherlands (chapter 6).

Figure 9: Example of a palatomaxillary reconstruction with a vascularized fibular composite free-flap [81].



Aim and outline of this thesis

The central aim of this thesis is to contribute to the improvement of various aspects of care for patients with MSCC.

Hence, this thesis focuses firstly on detection of bone invasion of the maxilla during preoperative assessment (chapters 1 and 2):

- In chapter 1, a diagnostic test accuracy study about the value of CT and MRI will be discussed.
- In chapter 2, a diagnostic test accuracy study about the value of Cone Beam CT in the outpatient clinic will be discussed.

Subsequently, this thesis focuses on currently known risk factors, local recurrence and overall survival for MSCC (chapter 3):

- In chapter 3, a systematic review and meta-analysis of the current literature will be discussed.
- Next, this thesis focuses on local recurrence and salvage surgery (chapter 4):
- In chapter 4, a retrospective analysis on risk factors associated with local recurrence and the value of salvage surgery will be discussed.

After which, this thesis will focus on risk factors and probability of overall mortality (chapter 5):

- In chapter 5, the development and internal validation of a prediction model that can calculate the probability of 2- and 5-year overall mortality will be discussed.

Furthermore, this thesis will focus on midfacial defect management (chapter 6):

- In chapter 6, a national e-survey about current methods of defect management in the Netherlands will be discussed.

Finally, the key findings and clinical implications of this study are summarized and discussed in the concluding section. A Dutch translation of the summary and discussion of this thesis is included.

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Chapter 1

Detecting Bone Invasion of the Maxilla by Oral Squamous Cell Carcinoma: Diagnostic Accuracy of Preoperative Computed Tomography Versus Magnetic Resonance Imaging

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Abstract

Purpose: For planning of the surgical resection, computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used for the preoperative assessment of bone invasion of the maxilla. The purpose of this study was to compare the diagnostic test accuracy of CT and MRI for detecting bone invasion of the maxilla in patients with squamous cell carcinoma of the maxilla (MSCC).

Materials and Methods: We conducted a retrospective cross-sectional study and enrolled a consecutive number of patients with primary MSCC between 2000 and 2017 who underwent either preoperative CT or MRI scans. The outcome variable was the absence or presence of bone invasion, with histopathologic examination of the resection specimen as the gold standard. The predictor variable was the imaging technique (CT and MRI). The imaging results on bone invasion were compared with the histopathologic results. Sensitivity and specificity were calculated, and the 2-sided Fisher exact test was used to calculate statistically significant differences between the unpaired CT and MRI results. Receiver operating characteristic curves were computed, and the area under the curve (AUC) was calculated.

Results: The study included 72 patients (29 male and 43 female patients) with a mean age of 72 years. A total of 41 CT scans and 31 MRI scans were available. Histopathologic examination showed bone invasion in 45 cases: 26 of 41 patients with CT scans (63%) and 19 of 31 patients with MRI scans (61%). CT yielded 2 false-positive and 2 false-negative results, with a sensitivity of 92%, specificity of 87%, and AUC of 0.895. MRI yielded 5 false-positive and 2 false-negative results, with a sensitivity of 89%, specificity of 58%, and AUC of 0.739. No significant differences were observed for sensitivity ($P > .999$) and specificity ($P = .185$).

Conclusions: In the absence of metallic dental restorations, CT could detect bone invasion more accurately than MRI in this study; however, the difference was not statistically significant. The imaging method of choice may depend on other situational factors.

Introduction

Oral squamous cell carcinoma originates from the oral mucosa and may invade the underlying bone. In case of squamous cell carcinoma of the maxilla (MSCC) the alveolar process of the maxilla or the hard palate may be affected. MSCC can grow even farther into the maxillary sinus or nasal cavity [1]. The preferred treatment for oral squamous cell carcinoma is surgery with the aim to remove the tumour completely [2, 3]. In the presence of bone invasion, resection of the tumour with "en bloc" resection of the affected bone is necessary to achieve adequate tumour-free surgical margins. Such resections may create large mid facial defects [4]. Large mid facial defects require additional reconstruction, such as an obturator prosthesis or reconstructive surgery [5,6], otherwise, loss of orofacial function and aesthetic mutilation can result in severely decreased quality of life [7]. A smaller resection may be possible in the absence of bone invasion. Management of these smaller defects is more straightforward compared with the large mid facial defects.

For adequate planning of the surgical resection of MSCC, reliable imaging methods for detecting bone invasion are essential. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are commonly used for the preoperative assessment of bone invasion. The diagnostic test accuracy of CT and MRI has been studied extensively for detecting bone invasion of the mandible by squamous cell carcinoma [8]. There are only a few articles on imaging of bone invasion of the maxilla.

The purpose of this study was to compare the diagnostic test accuracy of CT and MRI for detecting bone invasion of the maxilla.

The first aim was to compile a database with data from medical records of patients with MSCC. The second aim was to reassess the presence of bone invasion on all the CT and MRI scans with a specialised radiologist. The final aim was to use statistical analyses to calculate significant between-group differences, interobserver agreement and diagnostic test performance measures such as sensitivity and specificity. We hypothesized that CT would be superior to MRI as CT is assumed to be the best imaging method for the assessment of bony structures.

Materials and Methods

Study Design and Participants

The writing of this study [9] was performed in accordance with the STARD (Standards for Reporting Diagnostic accuracy) checklist [10] and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [11].

This study was deemed exempt by the Utrecht institutional review board owing to the retrospective nature of the study. All appropriate guidelines regarding data privacy and security were followed.

To address the research purpose, we designed and implemented a retrospective cross-sectional study. The study population was composed of all patients operated on consecutively for MSCC between January 2000 and April 2017.

The departmental database was used to identify potentially eligible patients. To be included in the study sample, patients had to receive a diagnosis of MSCC, originating from the mucosa, located on the alveolar process of the maxilla or the hard palate. Patients were excluded if they had histologic tumour types other than squamous cell carcinoma, had sinonasal tumours, or had absent CT and MRI scans. Patients also were excluded if imaging artifacts hindered adequate assessment of bone invasion.

Preoperative Screening

Preoperative screening included physical examination, rthopantomography, MRI scan and/or CT scan, chest radiograph, and ultrasound of the neck with fine-needle aspiration cytology on indication. Tumours were staged according to the TNM staging classification [12]. All cases were discussed in a weekly multidisciplinary team meeting. Treatment was determined according to national guidelines [13].

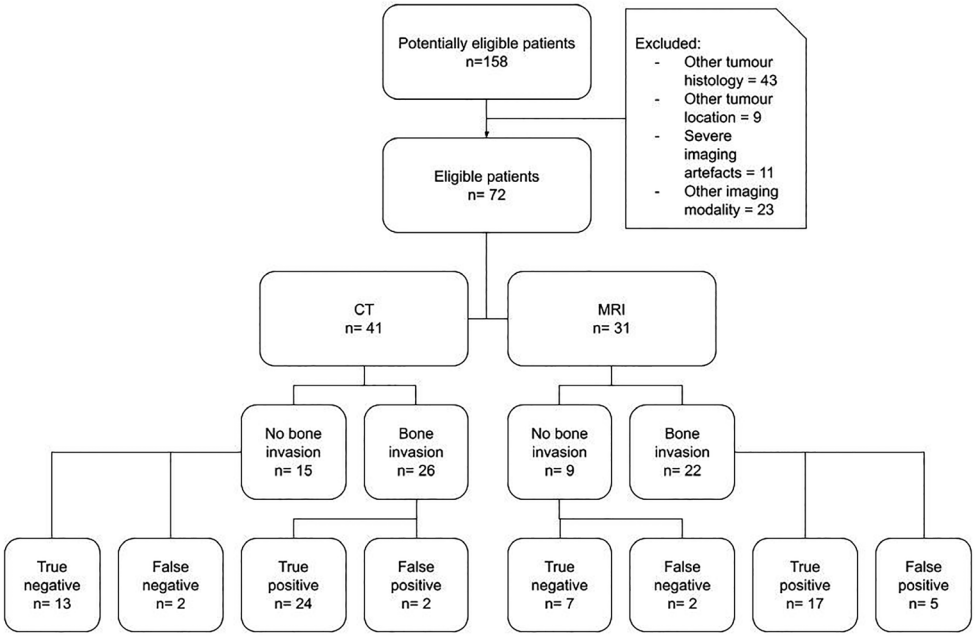
Computed Tomography

CT was performed on a 128–detector row CT scanner with 8 cm of coverage (iCT 256; Philips, Cleveland, OH) according to a standard protocol with intravenous injection of 150 mL of iohexol (Omnipaque, 350 mg/mL; GE Healthcare, Buckinghamshire, United Kingdom). Spiral CT was performed in the transversal and coronal planes, in contiguous 1.5-mm slices in areas of suspected bone invasion, reconstructing at both soft tissue and bone tissue settings. The presence of bone invasion was subsequently reported in standardized imaging reports by a dedicated head and neck radiologist.

Magnetic Resonance Imaging

MRI was performed on a 1.5-T magnetic resonance (MR) whole-body system (Philips, Best, the Netherlands) with a circularly polarized neck array coil according to a standard protocol. MR data acquisition consisted of fast spin echo T2-weighted images in the axial and coronal planes and spin echo T1-weighted images obtained before (axial plane) and after (axial and coronal planes) administration of contrast agent (gadopentetate dimeglumine, 0.2 mL/kg). All images were acquired with a 3.5-mm slice thickness. The presence of bone invasion was subsequently reported in standardized imaging reports by a dedicated head and neck radiologist.

Figure 1: Diagram of patient flow through study. CT, computed tomography; MRI, magnetic resonance imaging.



Surgery

All patients underwent surgery—either local resection or partial maxillectomy, hemimaxillectomy, or (sub)total maxillectomy—within 3 weeks of preoperative imaging.

Histology

The resection specimens were cut into 3-mm-thick buccolingual slices with a water-cooled, engine driven, circular, diamond-coated saw blade. The slices were decalcified in 10% formic acid, processed in paraffin wax, sectioned at 5 mm, and stained with hematoxylin-eosin. The slices were examined by a pathologist, specialized in head and neck oncology.

The presence of bone invasion was reported in standardized postoperative histopathologic reports.

Imaging Reassessment

For this study, a radiologist specialized in head and neck oncology (J.W.D.) and a researcher (F.J.B.S.) reassessed the CT scans and MR images for the presence of bone invasion of the maxilla while blinded from the original standardized imaging reports. Disagreements between the radiologist and researcher were resolved by discussion until consensus was reached.

On CT, bone invasion was defined as any disruption of the cortical bone adjacent to the abnormal soft tissue mass. On MRI, bone invasion was defined as either the absence of the typical hypointense signal on T1- or T2-weighted images of cortical bone or the replacement

of the hyperintense signal of medullary bone caused by the adjacent tumour signal, which is a hypointense signal on T1 imaging, hyperintense signal on T2 imaging, and/or the presence of contrast agent enhancement.

Statistical Analysis

To determine whether the CT group and MRI group were statistically comparable, differences between these groups were calculated with the independent samples t test for continuous variables and with the McNemar test, Pearson χ^2 test, or 2-sided Fisher exact test for nominal variables [14,15] Between-group differences were determined for the following variables: gender (male or female), mean age at operation (in years), tumour site (alveolar process or hard palate), T category (1, 2, 3, or 4), median tumour diameter on imaging, bone invasion on imaging, surgical procedure (local resection, partial maxillectomy, hemimaxillectomy, or subtotal maxillectomy), median tumour diameter on histology, and bone invasion on histology. Between-group differences were considered statistically significant at $P < .05$.

The Cohen κ was used to calculate agreement between the results of the imaging reassessment and the results of the original imaging reports [16] A κ value between 0.81 and 1.00 was considered very good agreement; κ between 0.61 and 0.80, good; κ between 0.41 and 0.60, moderate; κ between 0.21 and 0.40, fair; and κ of 0.20 or less, poor [14].

The results of the reassessment were used to calculate the diagnostic test accuracy of CT and MRI. The outcome variable was the absence or presence of bone invasion, with histopathologic examination as the gold standard. The predictor variable was the imaging technique (CT or MRI). The imaging results on bone invasion were compared with the histopathologic results. By use of cross tabulations, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, as well as 95% confidence intervals, were calculated. Receiver operating characteristic curves were computed, and the area under the curve (AUC) was calculated for CT and MRI. The AUC was considered excellent if 0.91 or greater, very good if between 0.81 and 0.90, good if between 0.71 and 0.80, sufficient if between 0.61 and 0.70, and poor if between 0.51 and 0.60 [17]. The χ^2 test or Fisher exact test was used to calculate the significance of differences between the sensitivities and specificities of CT and MRI. Differences were considered statistically significant at $P < .05$. Missing or indeterminate data were handled by pairwise deletion.

Sample Size Calculation

To detect statistically significant differences between the specificity results of CT and MRI with the χ^2 test, assuming $\alpha = .05$, $\beta = .1$, power of 90%, and $\delta = .29$ (87% – 58% = 29%), both groups required a minimum of 23 patients with true-negative and/or false positive results [18]. Analysis was aided by SPSS software (version 25.0 for Windows; SPSS, Chicago, IL).

Results

A total of 158 patients were potentially eligible for inclusion. Of these patients, 86 were excluded, whereas 72 patients were included in this study. Eleven patients were excluded because of extensive imaging artifacts that impaired adequate assessment of tumour bone invasion on CT. All these patients had multiple metal dental restorations. Of the patients, 41 had CT scans and 31 had MRI scans. None of the patients had both CT and MRI scans. Figure 1 shows the patient flow through the study. Table 1 shows the baseline characteristics. The proportion of female patients was significantly higher in the CT group than in the MRI group (P = .028). No other significant differences in the distribution of characteristics were found between the CT and MRI groups (Table 1).

Table 1: clinical data of CT and MRI groups.

Baseline characteristics	CT (n=41)	MRI (n=31)	p-value
Sex			
Male	12	17	
Female	29	14	.028
Mean age at operation (years)	72 (46 - 96)	71 (50 – 93)	.818
Tumour site			
Hard palate	15	8	
Alveolar process	26	23	.331
cT-stage			
T1	10	6	
T2	10	7	
T3	1	1	
T4	20	17	.942
Imaging median tumour diameter (mm)	25 (0 – 54)	25 (0 – 49)	.744
Imaging results			
No bone invasion	15	9	
Bone invasion	26	22	.501
Surgical procedure			
Local resection	6	2	
Partial maxillectomy	21	18	
Hemimaxillectomy	13	11	
Subtotal maxillectomy	1	0	.562
pT-stage			
T1	7	7	
T2	15	8	
T3	4	2	
T4	15	14	.689
Histology median tumour diameter (mm)	27 (2 – 66)	28 (9 – 68)	.388
Histological examination			
No bone invasion	15	12	
Bone invasion	26	19	.854

Table 2 shows an overview of patients with or without histologic bone invasion per characteristic for CT and MRI. For both CT (P > .999) and MRI (P = .242), gender was independent from bone invasion. In the CT group, tumours located at the alveolar process significantly more often had bone invasion than no bone invasion (P = .018). In the CT and MRI groups, the patient group with bone invasion had significantly more T4 tumours, larger tumour diameters, and larger resections.

Table 2: Overview of cases with or without histologic bone invasion per patient and tumour characteristics for CT and MRI.

Baseline characteristics	**CT (n=41)**			**MRI (n=31)**		
	No bone invasion (n = 15)	**Bone invasion (n = 26)**	**p-value**	**No bone invasion (n = 12)**	**Bone invasion (n = 19)**	**p-value**
Sex						
Male	4	8		5	12	
Female	11	18	>.999	7	7	.242
Mean age at operation (years)	71 (46 – 90)	72 (54 – 96)	.770	73 (50 – 93)	70 (50 – 92)	.516
Tumour site						
Hard Palate	9	6		3	5	
Alveolar Process	6	20	.018	9	14	>.999
cT-stage						
T1	7	3		3	3	
T2	7	3		6	1	
T3	0	1		1	0	
T4	1	19	<.0005	2	15	.001
Imaging median tumour diameter (mm)	13 (0 – 35)	30 (11 – 54)	<.0005	13 (0 – 26)	28 (12 – 49)	.012
Imaging results						
No bone invasion	13	2		7	2	
Bone invasion	2	24	>.999	5	17	.453
Surgical procedures						
Local resection	6	0		2	0	
Partial maxillectomy	9	12		10	8	
Hemimaxillectomy	0	13		0	11	
Subtotal maxillectomy	0	1	<.0005	0	0	.001
pT-stage						
T1	6	1		5	2	
T2	7	8		5	3	
T3	3	1		1	1	
T4	0	15	<.0005	1	13	.004
Histology median tumour diameter (mm)	23 (2 – 48)	34 (4 – 66)	.023	22 (9 – 35)	31 (13 – 68)	.057

The results of the reassessment and the standardized imaging reports differed in 3 cases. In 2 patients with CT scans, bone invasion was classified as positive in the reassessment but the standardized reports were inconclusive and subsequently classified bone invasion as negative. In 1 patient with an MRI scan, bone invasion was classified as positive in

the reassessment but negative in the standardized report. Consequently, the k value for the CT group was 0.898 (P < .0005), and the k value for the MRI group was 0.924 (P < .0005). Agreement between the reassessment and the standardized reports was therefore considered very good.

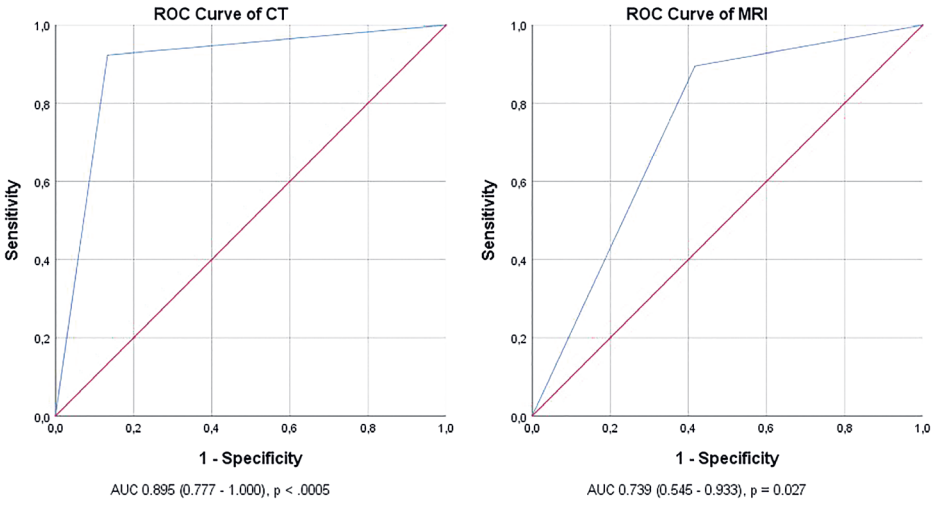
Table 3 shows the cross table with the imaging findings of the reassessment and histopathologic results of the resection specimens. Histopathologic examination of the resection specimens showed bone invasion in 45 cases: Bone was invaded in 26 of 41 patients with CT scans (63%) and in 19 of 31 patients with MRI scans (61%). CT yielded 2 false-positive and 2 false-negative results. Consequently, CT had sensitivity of 92%, specificity of 87%, PPV of 92%, NPV of 87%, and accuracy of 90%. MRI yielded 5 false-positive and 2 false negative results. MRI had sensitivity of 89%, specificity of 58%, PPV of 77%, NPV of 78%, and accuracy of 77%.

Table 3: Results of CT and MRI for detecting bone invasion in MSCC patients.

	Histology				**Histology**		
CT	**Positive**	**Negative**	**Total**	**MRI**	**Positive**	**Negative**	**Total**
Positive	24	2	26	**Positive**	17	5	22
Negative	2	13	15	**Negative**	2	7	9
Total	26	15	41	**Total**	19	12	31
Sensitivity	92% (95% CI 75-99%)			**Sensitivity**	89% (95% CI 67-99%)		
Specificity	87% (95% CI 60-98%)			**Specificity**	58% (95% CI 28-84%)		
PPV	92% (95% CI 77-98%)			**PPV**	77% (95% CI 63-87%)		
NPV	87% (95% CI 63-96%)			**NPV**	78% (95% CI 46-93%)		
Accuracy	90% (95% CI 77-97%)			**Accuracy**	77% (95% CI 59-90%)		

Receiver operating characteristic curves were computed for CT and MRI (Fig 2). The AUC of CT scans was excellent (0.895, P < .0005), and the AUC of MRI scans was good (0.739, P = .027). No statistically significant differences were observed for sensitivity (P > .999) or specificity (P = .185) between CT and MRI. No adverse events occurred during or after CT or MRI recording. There were no missing or indeterminate data.

Figure 2: Receiver operating characteristic (ROC) curve with area under the curve (AUC + 95% Confidence Interval) of CT and MRI.



Discussion

The purpose of this study was to compare the diagnostic test accuracy (e.g., sensitivity and specificity) of CT and MRI for detecting bone invasion of the maxilla by MSCC. We hypothesized that CT would be superior to MRI as CT is assumed to be the best imaging method for the assessment of bony structures. Although this study showed that CT had better test accuracy parameters, the hypothesis was rejected because CT and MRI did not show statistically significant differences in sensitivity (92% and 89%, respectively; P > .999) and specificity (89% and 58%, respectively; P = .185). This study showed that in the absence of metallic dental restorations, CT can detect bone invasion very accurately (AUC, 0.895) and MRI can detect bone invasion well (AUC, 0.739). Furthermore, this study showed that the interpretation of the imaging results is reliable (κ = 0.898 and κ = 0.924, respectively). Lee et al [19] (2014) evaluated MRI for detecting bone invasion by MSCC in 33 patients and reported a sensitivity of 83.0%, specificity of 83.4%, PPV of 64.5%, and NPV of 90.4%. Specificity in our sample was lower because our sample had more false-positive results. False-positive MRI results are often caused by inflammation and oedema around the tumour, which is a well-known limitation of MRI interpretation of bony involvement in oral cancer [20]. Ariyoshi and Shimahara [21] (2000) qualitatively evaluated CT and MRI for detecting bone invasion in a small sample of 14 patients with MSCC. They reported better depiction of subtle invasion of the maxillary bone by CT than by MRI. However, their imaging results were not compared with the histopathologic gold standard. Furthermore, they reported that CT was hindered by artifacts caused by metal dental restorations. In our study, 11 potentially eligible patients with CT scans were excluded because of artifacts caused by multiple metal dental restorations that severely hindered imaging assessment. None of the MRI scans had to be excluded because

of artifacts. In oral cancer, artifacts caused by metallic dental restorations on CT scans and, to a lesser extent, MRI scans are a recognized problem [22-24]. Dental restorations made from composite, ceramic, or temporary restorative materials seem to cause artifacts on CT scans as well [25]. Digital artifact reduction improves the quality of CT scans but does not preclude misinterpretation. Dual-energy CT may yield better images but is not always available [26]. MRI might, therefore, be better suited for patients with large dental restorations. To our knowledge, this comparative study has the largest sample of patients with MSCC who underwent either CT or MRI. Because of the low prevalence of MSCC, the sample size was still small. According to the sample size calculation, the sample of patients with true-negative and false-positive CT and MRI results was too small for χ^2 tests to adequately calculate statistically significant differences between specificities of CT and MRI [18]. The Fisher exact test is a suitable alternative test for smaller samples, but this test also failed to show a statistically significant difference ($P = .185$). The risk of time selection bias was considered small because most patients (69%) were operated on between 2010 and 2017. Unpaired comparative analysis of CT and MRI was performed, which has a higher risk of confounding than paired comparative analysis [27]. Paired comparative analysis was not feasible because none of the included patients underwent both CT and MRI scans during the preoperative screening. In our study, the CT group contained a significantly larger proportion of female patients than the MRI group (Table 1). However, gender appeared independent from bone invasion in the CT group ($P > .999$) and MRI group ($P = .242$). Because Ebrahimi et al [28] also did not find a correlation between gender and bone invasion in oral cancer, we considered the risk of confounding or effect modification limited and considered both groups statistically comparable. With no statistically significant difference found between CT and MRI for detecting bone invasion by MSCC, the imaging method of choice may depend on situational factors. For patients who are less cooperative or are claustrophobic, CT may be preferred because it takes less time to complete than MRI. Limited access to one modality or the other may play a role, with the aim to keep the preoperative screening period short. CT scans are generally cheaper than MRI scans. On the other hand, MRI has the advantage of creating fewer artifacts than CT. Finally, MRI lacks the radiation burden that CT has. In the future, a larger multicentre, prospective, paired comparative study could overcome the limitations of our study and show the difference in diagnostic accuracy between CT and MRI with fewer patients. Furthermore, new imaging modalities for detecting bone invasion by MSCC could be evaluated in the future. Cone-beam CT (CBCT), for instance, is suitable for detecting bone invasion of the mandible [29]. For the detection of bone invasion of the maxilla, CBCT seems a promising imaging modality as well. CBCT is convenient because it can be performed at the patient's first visit in the outpatient clinic and has a lower radiation burden than regular CT. Positron emission tomography–CT is another modality to consider, given its prevalence in head and neck cancer staging. In the absence of metallic dental restorations, CT could detect bone invasion more accurately than MRI in this study; however, the difference was not statistically significant. The imaging method of choice may depend on other situational factors.

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Chapter 2

Value of Cone Beam Computed Tomography for Detecting Bone Invasion in Squamous Cell Carcinoma of the Maxilla

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Abstract

Objectives: To determine the diagnostic value of cone beam computed tomography (CBCT) for the detection of bone invasion in maxillary squamous cell carcinoma (MSCC).

Methods: A retrospective cohort study was conducted of consecutive patients with primary MSCC operated between September 2013 and August 2018, who had preoperative CBCT scans. CBCTs were assessed by a single surgeon (assessment 1), and by one surgeon with two researchers in consensus (assessment 2). The predictor variable was bone invasion on CBCT imaging. The outcome variable was bone invasion on histopathological examination. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, area under the curve (AUC) and Cohen's κ were calculated.

Results: Twenty-seven patients were included; histopathological examination showed bone invasion in 19 patients (70%). Assessment 1 yielded 13 true positive, 6 true negative, 2 false positive and 6 false negative results, resulting in 68.4% sensitivity, 75.0% specificity, 86.7% PPV, 50.0% NPV, 70.4% accuracy and .717 AUC. All results of assessment 2 were true positive and true negative, resulting in 100% sensitivity, specificity, PPV, NPV, accuracy and 1 AUC. The results of assessment 1 and assessment 2 differed in 6 cases. The κ was .38 (95% CI 0.04 – 0.72), p = .04.

Conclusion: Accuracy of CBCT was high, but observer-dependent. Standardisation of reporting may improve the quality of interpretation.

Introduction

Squamous cell carcinoma of the maxilla (MSCC) usually originates from the mucosa of the alveolar process or hard palate. It can invade the adjacent bone and subsequently grow into the maxillary sinus or nasal cavity [1]. The preferred treatment is complete surgical removal of the tumour [2, 3]. The preoperative extent of bone invasion involving the maxilla may be difficult to predict. Therefore, a reliable imaging method for preoperative detection of bone invasion is important, to keep the resection limited. For preoperative imaging, computed tomography (CT) imaging is often used for detecting maxillary bone invasion [4-6].

Cone beam computed tomography (CBCT) is an interesting alternative to conventional spiral CT imaging. A CBCT scanner produces a cone-shaped X-ray beam that captures the image in one swoop, as opposed to multiple conjoined images continuously recorded during spiral CT scanning [7]. CBCT imaging requires less time, produces lower radiation dosage and generates higher spatial resolution. Furthermore, patients are not required to lay down, but can sit with their head in the natural position during the scanning procedure [8].

Because of these advantages, CBCT rapidly gained popularity in the last two decades in multiple fields of dentistry and in oral and maxillofacial surgery. This is why the potential value of CBCT in preoperative detection of bone invasion by oral cancer is a subject of interest [8]. The value of CBCT for detecting bone invasion of the mandible has been studied [9, 10], but to the best of our knowledge, there are no studies that focused on the maxilla.

Therefore, the aim of this study is to determine the diagnostic value of CBCT for detecting bone invasion by MSCC. Our hypothesis is that the diagnostic value of CBCT for detecting bone invasion in MSCC is high and that the interobserver agreement is good.

Methods

A retrospective cohort study was conducted. This study was exempted from ethical review in writing by the 'IRB Utrecht', because of its retrospective design. Furthermore, this study followed the guidelines set out in the Helsinki Declaration.

This study was written in accordance with the 'standards for the reporting of diagnostic accuracy studies' (STARD) criteria [11] and 'strengthening the reporting of observational studies in epidemiology' (STROBE) guidelines [12].

Consecutive patients operated for MSCC between September 2013 and August 2018, who had a preoperative CBCT scan, were identified with the departmental database. To meet the inclusion criteria, the MSCC had to originate from the mucosa located on the maxillary alveolar process or the hard palate. Patients were excluded if they had other histological tumour types, or if they had sinonasal tumours. Patients were also excluded if their CBCT scans were not adequately assessable, due to imaging artefacts.

Preoperative evaluation

Standardized preoperative diagnostic work-up included physical examination, radiological imaging, and ultrasound of the neck with fine needle aspiration cytology on indication. For tumours localized near/ in the maxillary alveolar process, an orthopantomogram and CBCT was performed. For staging of the neck, MRI was performed of the head and neck area including the maxilla. Spiral CT of the head and neck area was performed in case MRI was contraindicated, for instance because of the presence of metallic dental restorations which could cause imaging artefacts or claustrophobia. In case bone invasion could not be excluded with MRI, an additional CBCT scan was performed.

The TNM-staging classification [13] was used to stage all the diagnosed tumours. A multidisciplinary team discussed all the cases in a weekly meeting. Subsequent treatment decision-making followed the Dutch national guidelines [14].

CBCT

CBCT was performed with the classic i-CAT scanner (Imaging Sciences International, Inc, Hatfield, PA, USA), and with i-CAT vision software version 1,9.314. The scanning settings of the i-CAT were standardised: the regular scan time was 1.8 seconds with a tube current of 8.2 mAs. The kilovoltage peak was 120kVp and the field of view (FOV) was either FOV10x5 for normal sized tumours, or FOV12x8 for large and/or dorsally located tumours.

All patients were scanned in the seated position, with their heads in a natural position.

Surgical treatment

Within 3 weeks of the preoperative evaluation, all patients underwent surgical treatment. The surgical procedure was either local resection, partial maxillectomy, hemimaxillectomy or (sub)total maxillectomy.

Histology

Standardised histopathological analysis of the postoperative resection specimens was conducted after every surgical procedure. The resection specimens were cut into 3 mm-thick buccopalatal slices with a water-cooled engine-driven circular diamond-coated saw blade. The slices were decalcified in 10% formic acid. The formalin-fixed paraffin-embedded tissue was sectioned at 5µm and stained with haematoxylin and eosin in a standard way. A specialised head and neck oncology pathologist examined the slides. The findings, like presence of bone invasion, were reported in a standardized histopathological report.

Imaging assessment 1

Assessment 1 was performed by a single surgeon (JVG) who assessed the CBCT scans. The reviewer was blinded from the original imaging reports and histopathological results. Bone invasion was defined as any disruption of the cortical bone adjacent to the abnormal soft-tissue mass and categorized as present or absent.

Imaging assessment 2

To simulate a clinical scenario of a discussion between colleagues, the images were jointly rated by multiple observers.

Assessment 2 was performed by one surgeon (EMVC) and two researchers (MGS and SF) who assessed the CBCT scans. The reviewers of assessment 2 were blinded from the original imaging reports and histopathological results as well.

Bone invasion was categorized as absent, presence of cortical interruption, or presence of cortical interruption and invasion into maxillary sinus and/or nasal cavity. Disagreements between the surgeon and researchers were resolved by discussion until consensus was reached.

The results of assessment 1 and 2 were used to calculate the diagnostic test efficacy of CBCT. The predictor variable was the presence of bone invasion on the CBCT images. For the statistical analyses, the results from imaging assessment 2 were dichotomized as absent (no cortical interruption) or present (i.e., both cortical interruption and invasion into maxillary sinus and/or nasal cavity).

The outcome variable was the absence/presence of bone invasion on histopathological examination of the resection specimens. Using cross tabulations, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and their 95% confidence intervals were calculated.

Receiver Operating Characteristics (ROC) curves were computed and the Area Under the Curve (AUC) was calculated. The AUC was considered excellent if ≥ 0.91, very good if 0.81 – 0.90, good if 0.71 – 0.80, sufficient if 0.61 – 0.70, and bad if 0.51 – 0.60 [15].

Agreement between the results of imaging assessment 1 and imaging assessment 2 was calculated with Cohen's kappa (κ).

The agreement was considered very good if κ was 0.81-1.00, good if κ was 0.61-0.80, moderate if κ was 0.41-0.60, fair if κ was 0.21-0.40, and poor if κ was <0.20 [16]. Missing or indeterminate data was handled by pairwise deletion.

Sample size calculation

The study aimed to determine interobserver agreement for the CBCT imaging assessments. The researchers hypothesized that the minimum value for the Cohen's kappa coefficient was 0.6 (K2=0.6), versus the null hypothesis of no agreement (K1=0). When the power and alpha were pre-specified at 80.0% and 0.05 respectively, a minimum sample of 20 cases was required for the detection of a minimum value of kappa 0.6 while holding the assumption that the proportion of ratings in agreement by both raters in each category was assumed to be directly proportional to one another [17].

Analysis was aided by the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS Inc., Chicago, USA).

Results

Sixty patients were potentially eligible for inclusion. Twelve patients with other tumour types, were excluded and 21 patients were excluded because they had no preoperative CBCT scan. In total, 27 patients were included (Figure 1).

Figure 1: Flow Chart of the included patients and assessment 1 and 2.

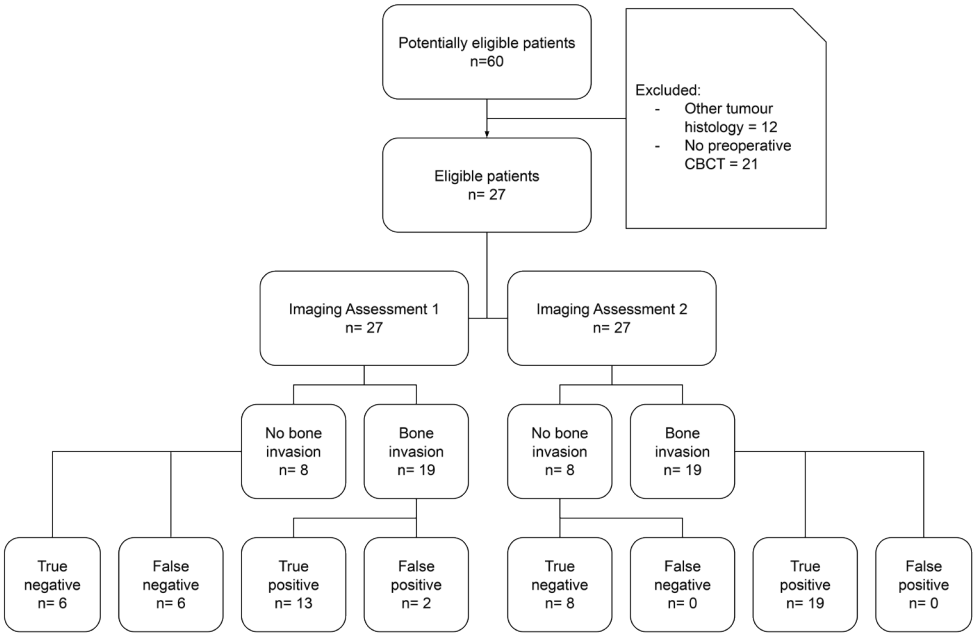


Table 1 shows the baseline characteristics of the study population. There were 7 male patients (26%) and 20 female patients (74%). Age at the time of operation ranged from 38 to 92 years. The most frequent tumour location was the alveolar process (81%). There were 11 pT1 tumours (41%), 5 pT2 tumours (19%), 2 pT3 tumours (7%) and 9 pT4 tumours (33%). The tumour diameters ranged from 1 to 68 mm.

Table 1: baseline characteristics.

Patient	Year of operation	Sex	Age at operation (years)	Tumour site	T-stage	Imaging assessment 1	Imaging assessment 2	Results histological examination	Histology tumour diameter (mm)
1	2013	Male	67	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	30
2	2014	Female	66	Alveolar process and hard palate	T4	Bone invasion	Bone invasion	Bone invasion	28
3	2014	Male	76	Alveolar process	T2	No bone invasion	Bone invasion	Bone invasion	21
4	2014	Female	60	Hard Palate	T1	No bone invasion	No bone invasion	No bone invasion	12
5	2014	Female	90	Alveolar process	T1	No bone invasion	No bone invasion	No bone invasion	9
6	2015	Female	50	Alveolar process	T1	Bone invasion	Bone invasion	Bone invasion	16
7	2016	Male	68	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	44
8	2016	Female	71	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	24
9	2016	Male	69	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	24
10	2016	Male	38	Alveolar process	T1	Bone invasion	Bone invasion	Bone invasion	14
11	2016	Female	92	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	68
12	2017	Female	46	Alveolar process	T1	Bone invasion	No bone invasion	No bone invasion	12
13	2017	Female	83	Alveolar process	T4	No bone invasion	Bone invasion	Bone invasion	23
14	2017	Female	54	Alveolar process	T2	Bone invasion	No bone invasion	No bone invasion	25
15	2017	Female	52	Hard palate	T1	No bone invasion	Bone invasion	Bone invasion	19
16	2017	Female	62	Alveolar process	T1	Bone invasion	Bone invasion	Bone invasion	13
17	2017	Male	78	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	28
18	2017	Female	85	Alveolar process	T3	Bone invasion	Bone invasion	Bone invasion	33
19	2017	Female	72	Alveolar process	T1	No bone invasion	No bone invasion	No bone invasion	5
20	2017	Female	78	Alveolar process	T4	Bone invasion	Bone invasion	Bone invasion	55
21	2017	Female	73	Alveolar process	T1	Bone invasion	Bone invasion	Bone invasion	4
22	2017	Female	85	Alveolar process	T2	Bone invasion	Bone invasion	Bone invasion	35
23	2017	Female	65	Alveolar process	T1	No bone invasion	No bone invasion	No bone invasion	2
24	2017	Female	43	Alveolar process	T2	No bone invasion	No bone invasion	No bone invasion	23
25	2018	Female	83	Alveolar process and hard palate	T1	No bone invasion	No bone invasion	No bone invasion	1
26	2018	Female	88	Hard palate	T2	No bone invasion	Bone invasion	Bone invasion	20
27	2018	Male	67	Alveolar process	T3	Bone invasion	Bone invasion	Bone invasion	30

The results of assessment 1 and 2 are listed in Table 2. Histopathological examination of the resection specimens showed bone invasion in 19 patients (70%). Assessment 1 yielded 13 true positive, 6 true negative, 2 false positive, 6 false negative results, which resulted in 68.4% sensitivity, 75.0% specificity, 86.7% PPV, 50.0% NPV and 70.4% accuracy. Assessment 2 yielded only true positive results, which resulted in 100% sensitivity, 100% specificity, 100% PPV, 100% NPV and 100% accuracy.

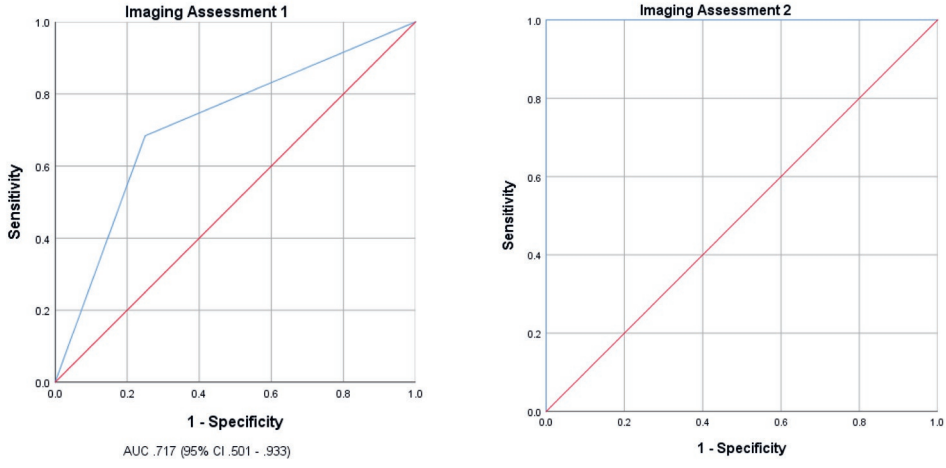
ROC-curves were computed for assessment 1 and 2 (Figure 2). AUC of assessment 1 was good (.717) and AUC of assessment 2 was excellent (1.000).

The results of assessment 1 and assessment 2 were different in 6 cases. Consequently, the κ for the interobserver agreement was .38 (95% CI 0.04 – 0.72), p = 0.038. The interobserver agreement was therefore deemed fair.

Table 2: diagnostic test results of assessment 1 and 2 of the CBCT images.

	Histology				Histology		
Imaging Assessment 1	**Positive**	**Negative**	**Total**	**Imaging Assessment 2**	**Positive**	**Negative**	**Total**
Positive	13	2	15	**Positive**	19	0	19
Negative	6	6	12	**Negative**	0	8	8
Total	19	8	27	**Total**	19	8	27
Sensitivity	68.4% (95% CI 43.5 – 87.4%)			**Sensitivity**	100% (95% CI 82.4 - 100%)		
Specificity	75.0% (95% CI 35.0 – 96.8%)			**Specificity**	100% (95% CI 63.1 – 100%)		
PPV	86.7% (95% CI 65.3 – 95.7%)			**PPV**	100%		
NPV	50.0% (95% CI 31.6 – 68.4%)			**NPV**	100%		
Accuracy	70.4% (95% CI 50.0 – 86.3%)			**Accuracy**	100% (95% CI 87.2 - 100%)		
AUC	.717 (95% CI .501 - .933)			**AUC**	1		

Figure 2: Receiver Operating Characteristics (ROC) curves and the Area Under the Curve (AUC) results.



Discussion

The results of assessment 1 were good (sensitivity 68.4%, specificity 75.0%, PPV 86.7%, NPV 50.0%, Accuracy 70.4%, AUC .717). The results of assessment 2 were excellent (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, Accuracy 100%, AUC 1). These results suggest that CBCT is of value for the detection of maxillary bone invasion by MSCC, but the results are observer-dependent.

There are two main causes of observer-dependent differences. The first cause is differences in training and experience of the observers. Repeated training has been shown to improve the interpretation of the imaging of several anomalies [18-20]. All observers in this study had been trained and were experienced in interpreting CBCT scans. Moreover, assessment 2 with multiple observers scoring in consensus, yielded 100% sensitivity and specificity, which suggests that joint evaluation of the scans and discussion improves the diagnostic accuracy.

The second cause of observer-dependent differences may be the (lack of) scoring criteria. Standardised scoring and reporting have been shown to improve the interpretation of scans of the appendix, pulmonary oedema and adnexal masses [21, 22, 23]. Standardized reporting helps with the correct interpretation of imaging in general [24]. To the best of our knowledge, there are no studies on the value of standardised scoring and reporting of scans for oral cancer yet. In our study, the highest accuracy was reached when the scans were assessed with the largest number of pre-defined categories in assessment 2. So, our results suggest, that using a number of specific criteria improves the interpretation of CBCT imaging for bone invasion by MSCC.

As yet, clear peer-reviewed guidelines are lacking for the interpretation and reporting of CBCT images of oral cancer. Formats for structured reporting of CT and MRI images have been widely adopted to describe the location of the primary tumour, the extent of soft tissue involvement, the extent of bony involvement and the nodal status [25]. Similar formats for CBCT reports are not in place yet.

High quality imaging reports should be ‘accurate’, ‘clear’, ‘complete’ and ‘timely’ [26]. A CBCT report format has been proposed for use in general practice [27]. This format mentions all anatomical subheadings that may be depicted on a CBCT scan: paranasal sinuses, nasal cavity, airway, cervical spine, temporomandibular joint, dental findings, other findings and recommendations. In this way, the observer is forced to analyse every section of the CBCT image and to report findings in a standardised way, without being forced to complete inefficient and time-costly formats.

The accuracy of CBCT for detecting bone invasion in MSCC and the interobserver agreement may improve by incorporating the essential CT/MRI reporting requirements of oral tumours (primary tumour dimensions, soft tissue involvement, bony involvement, nodal status) [25] into the CBCT report format as proposed by Miles et al. [27]. Whether standardized

reporting helps to improve the accuracy and interobserver agreement of CBCT in detecting bone invasion, needs to be evaluated in the future.

A recent systematic review compared the detection accuracy of CBCT with the more conventional reconstructive imaging techniques CT, MRI, single-photon emission tomography (SPECT), multi-slice computed tomography with contrast (MSCT), and panoramic radiography (PR) [8]. In this systematic review, two studies reported the results of bone invasion detection by CBCT. One study assessed bone invasion of the mandible by squamous cell carcinoma, for which the CBCT had 93% sensitivity, 62% specificity and 78% accuracy [10]. The second study assessed bone invasion of the mandible by oral tumours located in the floor of mouth, retromolar area and lower alveolar process, for which the CBCT had 90.9% sensitivity, 100% specificity and 95.7% accuracy [9]. Lastly, the NPV of CBCT (89.83%) and SPECT (95.53%) for the detection of bone invasion of the mandible was much higher than the NPV of CT, MRI, MSCT and PR in this systematic review [8]. These results and the results of our study suggest that the CBCT is of value for the assessment of bone invasion of the mandible and maxilla.

Limitations

This study was limited by its relatively small sample size, due to the very low incidence of MSCC, the retrospective design, and the low number of patients who had received preoperative CBCT scans. Out of 60 potentially eligible patients, 21 patients did not have a preoperative CBCT-scan, because they had either spiral CT or MRI, or a combination of the two. Nevertheless, for the purposes of this study, the sample size was deemed sufficient.

Even though histopathological assessment for bone invasion is presented as the gold standard, the diagnosis of true histological bone invasion can be challenging, especially in cases with the more erosive type of invasion with a pushing border front [28].

Conclusion

The accuracy of CBCT for the detection of bone invasion in MSCC patients was high, but observer-dependent. Scoring in consensus and standardisation of interpretation and reporting of CBCT images may improve detection of bone invasion and are subjects for further study.

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Chapter 3

Local Recurrence and Survival after Treatment of Oral Squamous Cell Carcinoma of the Maxilla: a Systematic Review and Meta-Analysis

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Abstract

Objectives: Oral squamous cell carcinoma involving the maxilla (MSCC) is a rare malignancy. The aim was to perform a systematic review and meta-analysis of available literature on local recurrence (LR), overall survival (OS) and associated risk factors of MSCC.

Study Design: The Cochrane, PubMed and EMBASE databases were searched with related keywords and synonyms. The pooled proportions of both LR and OS were subsequently calculated with 95% confidence intervals.

Results: 2638 articles were screened on title and abstract, 131 articles were screened full-text, and 20 were included. The pooled 5-year LR rate was 19.3%, and the 5-year OS rate was 53.7%. The subgroup analysis between surgery only and surgery with (neo)adjuvant treatment resulted in: OR .76 (95% CI .41 – 1.40).

Conclusions: Postoperative (chemo)radiotherapy or preoperative intra-arterial chemoradiotherapy improves survival when adverse tumour characteristics are present. Posterior tumour extension into the soft palate, pterygoid muscle, pterygoid process and infratemporal fossa was significantly associated with decreased OS in multiple studies. More research into the risk-reduction of local recurrence is warranted.

Introduction

Squamous cell carcinoma involving the maxilla (MSCC) is a rare subtype of oral cancer. It originates from epithelial cells lining the oral cavity, starting at the maxillary alveolus or hard palate. MSCC usually causes symptoms like tumorous lesions, non-healing wounds and ill-fitting dentures in the early stage.

Surgical treatment is the gold standard for oral MSCC and is accompanied by (neo-) adjuvant treatment on indication, depending on tumour stage and cervical lymph node involvement. Complete resection of the maxillary tumour is the primary goal but can be challenging due to the complex anatomy, poor visibility and poor access. Incomplete resection of large tumours and subsequent local recurrence account for a large proportion of patient mortality in MSCC. Moreover, various survival-related risk factors have been identified for MSCC [1, 2]. Unfortunately, research on this rare subsite of oral cancer is still scarce.

This study aimed to perform a systematic review and meta-analysis of available data on surgical treatment outcomes (i.e., local recurrence (LR), overall survival (OS) for patients with MSCC. The second objective was to identify factors associated with LR and OS.

Materials and Methods

This study was conducted using a systematic review protocol (PRISMA) [3].

A systematic search was performed using the Cochrane, PubMed and EMBASE databases for original relevant articles, published until the 4th of June 2021. A combination of keywords, MeSH terms and Emtree terms were used to search for titles and abstracts in the databases.

The keywords “squamous cell carcinoma of the maxilla”, “surgical treatment”, “local recurrence”, “overall survival”, “risk factors”, and their synonyms were used. Human studies with available full-text articles were potentially eligible if they reported on the surgical treatment for MSCC and reported on the primary outcomes of LR and OS and associated risk factors after a 5-year follow up. Study designs like other systematic reviews or case reports were excluded. Studies with wrong domains (e.g., mandibular tumours), or wrong determinants (e.g., mandibulectomy) or wrong outcomes (e.g., quality of life) were also excluded. After removing duplicates, two authors (FJBS & DAAR) independently screened all titles and abstracts according to the predefined inclusion and exclusion criteria. If there was disagreement, then consensus was reached by discussion. The resulting full-text articles were then screened in detail for final selection. Snowballing was performed by checking all citations and references in the full-text articles for missed studies in the systematic search. The two authors independently extracted data from the included studies using standardised data extraction forms. In case of disagreement, a consensus was reached by discussion.

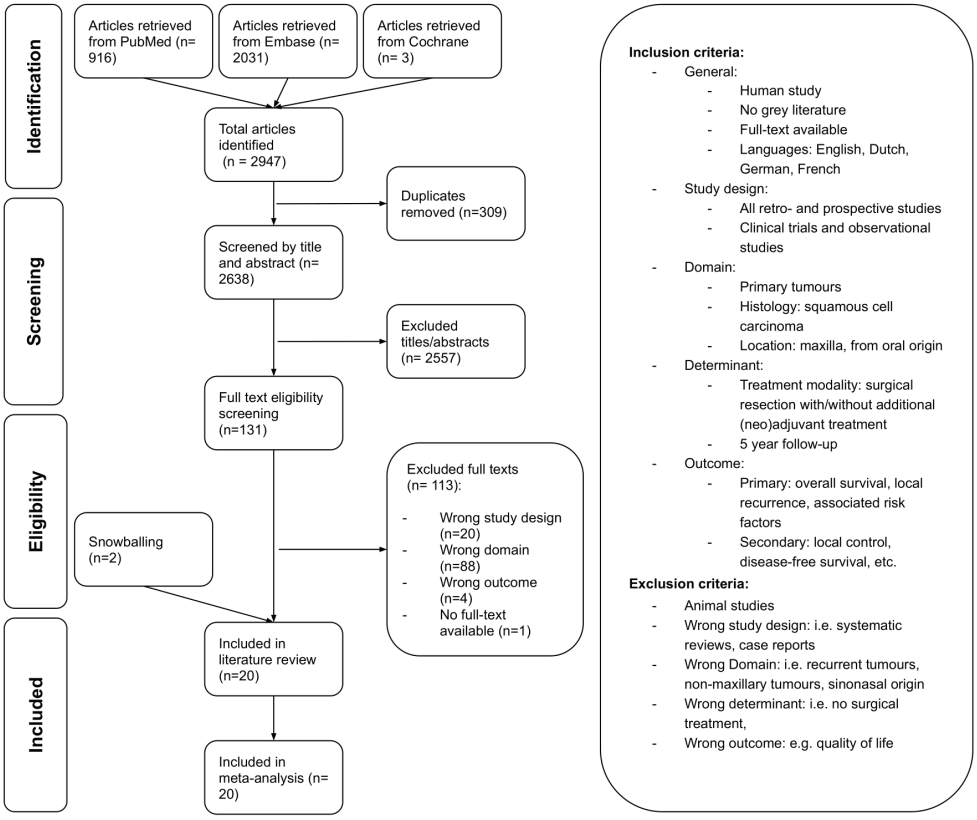
The following data variables were extracted if present: first author, publication year, study type, inclusion period, sample size, primary tumour location, tumour stage, histology, treatment modalities, follow-up length, primary outcome variables (LR rate, OS rate), secondary outcome variables, associated risk factors, statistical methods, the total number of patients with LR and finally the total number of surviving patients. In the case of missing outcome variables, data were synthesised from raw data when sufficiently available. In case outcome data could not be synthesised from raw data, then the particular study would not be included in that specific analysis. The quality assessment of the individual studies was done by the two authors independently, using the Newcastle-Ottawa scale for non-randomised studies [4]. A quality score was calculated as the sum of all the scores in the assessment (max. 9). Higher scores indicate higher quality and lower risk of bias. Studies with scores <7 were considered of low quality. Low-quality studies were not included in the meta-analysis. Two outcomes were of interest in the meta-analysis: the 5-year LR rate and the 5-year OS rate. The 5-year LR rate was defined as the percentage of patients who developed tumour recurrence at the primary tumour site within 5 years of surgical treatment, and the percentage of patients who survived 5 years after surgical treatment was defined as the 5-year OS rate.

Funnel plots were computed to assess the presence of reporting biases. Tests of heterogeneity were performed with the inconsistency index (I^2). The I^2 cut-off values of <30%, 30-59%, 60-75% and >75% were used to indicate low, moderate, substantial and considerable heterogeneity respectively [5, 6]. If the heterogeneity was significant (p< .05), the random-effects model was emphasised in the meta-analysis to account for the random variation within studies and the variation between different studies [7]. The pooled proportions of both LR and OS were subsequently calculated with 95% confidence intervals [6, 8], and forest plots were computed with the results of all studies in chronological order. The data that support the findings of this study are available from the corresponding author upon reasonable request. Statistical analyses were performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

The flowchart of the search is presented in Figure 1. The combined search in Cochrane, PubMed and EMBASE yielded 2947 articles. After removing 309 duplicates, 2638 titles and abstracts were screened, and 2557 articles were excluded. After that, 131 studies were eligible for full-text screening. Subsequently, 111 articles were excluded after the full-text screening, mainly because the study designs and the domains were incompatible. In total, 20 articles were included after the completion of the literary search.

Figure 1: Flowchart of the literary search.



Study Characteristics

An overview of all the included studies and their characteristics is presented in Table 1 [2, 9-27]. All 20 included studies were observational. The results of the quality assessment are presented in Table 2. All articles were of good quality. The publication years of the included articles ranged from 2008 to 2020, with reported inclusion periods ranging from 1975 to 2018. Sample sizes varied between 20 – 199 patients. The sum of all included MSCC patients is 1531 (the samples of Slieker et al. [2] and Slieker et al. [27] are the same and therefore counted once). All studies had solely included patients with squamous cell carcinoma. Most studies presented their data on tumour staging, except for one study [25]. The proportion of patients with advanced tumour stages (T3-4) was 731/1447 (51%), and early tumour stages (T1-2) was 716/1447 (49%).

Treatment modalities of 1185/1531 (77%) patients were specified and 346/1531 (23%) were not [12, 16, 21, 24]. Nine different treatment modalities were reported: 748/1185 (63%) patients had surgery only, 277/1185 (23%) had surgery with postoperative radiotherapy, 51/1185 (4%) had surgery with postoperative (chemo)radiotherapy, 40/1185 (3%) had preoperative intra-arterial chemotherapy with radiotherapy and surgery, 10/1185 (0.8%)

had preoperative intravenous chemotherapy with radiotherapy and surgery, 3/1185 (0.3%) had preoperative radiotherapy with surgery, 27/1185 (2%) had no surgery and chemoradiotherapy, 19/1185 (2%) had no surgery and radiotherapy only, and 10/1185 (0.8%) patients had palliative treatment.

Primary radiotherapy or chemoradiotherapy was performed with curative intent in 28/46 (61%) patients [9, 10, 20], with palliative intent in 3/46 (7%) patients [9], while 3/46 (7%) patients refused surgery [20] and in 12/46 (26%) patients the reason was unspecified [9, 25, 26]. In any event, patients who had primary radiotherapy or chemoradiotherapy had significantly lower survival rates compared to patients with primary surgical treatment [9, 10, 20].

The following indications for postoperative radiotherapy in 155/277 (56%) patients were listed:

Advanced tumour stage [11, 13, 14, 19, 20, 22-24], close/positive surgical margins (after reresection) [11, 13-15, 19, 22-24], cervical lymph node involvement [13-15, 19], extracapsular spread [13-15, 20], bone/vascular/perineural invasion and non-cohesive growth [19, 20, 22]. The indication for postoperative radiotherapy was not specified for 104/259 (40%) patients [9, 10, 17, 18, 25].

The reported indications for surgery with postoperative chemoradiotherapy were similar to the indications for postoperative radiotherapy [19, 20, 23, 27]. One study specified that chemotherapy was contraindicated if the patient was >70 years or had any other contraindications for chemotherapy [27].

One study administered preoperative intravenous chemoradiotherapy followed by surgery in 10 patients because of the advanced tumour stage and found a significant correlation between LR and preoperative chemoradiotherapy [23]. However, exact treatment regimens were not reported.

Another study used preoperative intra-arterial chemotherapy followed by surgery to treat 40 patients with T2-4 stage tumours and tumour involvement of the soft palate, pterygoid muscle, and pterygoid process [26].

Preoperative intra-arterial chemoradiotherapy was conducted with fluorouracil 100 – 300 mg daily for 21 days via cannulation of the superficial femoral artery. Furthermore, 42 patients with T1-2 tumours located anteriorly were treated with surgery only [26].

Table 1: Overview of included studies; RT= radiotherapy, Ch= chemotherapy, ChRT= chemoradiotherapy, (Ch)RT= chemotherapy and/or radiotherapy, intra-art= intra-arterial.

First author	Publication year	Inclusion period	Sample size (n=)	Histological tumour type	T-stage of SCC-tumours	Treatment modalities of SCC tumours	5yr local recurrence rates	5yr overall survival outcomes
Binahmed et al [9]	2008	1975 - 2004	37	Only SCC	T1 = 6 T2 = 9 T3 = 4 T4 = 15 Lost = 3	Surgery only = 14 Surgery with postop. RT = 9 RT only = 5 ChRT = 1 Palliative treatment = 8	6/37 (16%)	12/37 (33%)
Wang et al [10]	2010	1997 - 2007	79	Only SCC	T1 = 4 T2 = 28 T3 = 24 T4 = 23	Surgery only = 37 Surgery with postop. RT = 18 (Ch)RT = 24	37/79 (47%)	27/79 (34%)
Ramalingam et al [11]	2011	1999 - 2009	24	Only SCC	T1 = 3 T3 = 9 T4 = 12	Surgery only = 9 Surgery with postop. RT = 15	N/A	6/24 (25%)
Poeschl et al [12]	2011	1992 - 2007	93	Only SCC	T1 = 9 T2 = 14 T3 = 9 T4 = 61	86 Patients had surgery and some had postop. RT, but it is not specified exactly how many had postop. RT. (Ch)RT = 7	N/A	66/93 (71%)
Meng et al [13]	2012	2003 - 2009	78	Only SCC	T1 = 21 T2 = 25 T3 = 3 T4 = 29	Surgery only = 46 Surgery with postop. RT = 32	7/78 (9%)	39/78 (50%)
Eskander et al [14]	2013	1994 - 2008	97	Only SCC	T1 = 15 T2 = 28 T3 = 5 T4 = 49	Surgery only = 67 Surgery with postop. RT = 30	12/97 (12%)	43/97 (44%)
Dalal et al [15]	2013	2000 - 2010	30	Only SCC	T1 = 1 T2 = 2 T3 = 2 T4 = 25	Surgery only = 15 Surgery with postop. RT = 15	4/30 (13%)	10/30 (66.7%)
Feng et al [16]	2013	1998 - 2011	129	Only SCC	T1 = 27 T2 = 39 T3 = 21 T4 = 42	All patients had surgery, some had postop. RT, but not specified exactly	29/129 (22%)	73/129 (56.5%)

Table 1: Continued.

First author	Publication year	Inclusion period	Sample size (n=)	Histological tumour type	T-stage of SCC-tumours	Treatment modalities of SCC tumours	5yr local recurrence rates	5yr overall survival outcomes
Yang et al [17]	2015	2003 - 2012	62	Only SCC	T1 = 8 T2 = 20 T3 = 19 T4 = 15	Surgery only = 49 Surgery with postop. RT= 13	14/62 (23%)	35/62 (57%)
Givi et al [18]	2016	1985 - 2011	199	Only SCC	T1 = 76 T2 = 53 T3 = 6 T4 = 64	Surgery only = 155 Surgery with postop. RT = 44	37/199 (19%)	135/199 (68%)
Koshkavera et al [19]	2016	Not specified	20	Only SCC	T1 = 3 T2 = 9 T3 = 6 T4 = 2	Surgery only = 8 Surgery with postop. RT = 7 Surgery with postop. ChRT = 5	4/20 (20%)	10/20 (50%)
Morice et al [20]	2016	2006 - 2013	47	Only SCC	T1 = 6 T2 = 5 T3 = 1 T4 = 35	Surgery only = 19 Surgery with postop. RT = 13 Surgery with postop. (Ch)RT = 8 RT only = 3 ChRT only = 2 Palliative treatment = 2	N/A	15/47 (32%)
Troeltzsch et al [21]	2016	2006 - 2013	92	Only SCC	Tis = 1 T1 = 26 T2 = 25 T3 = 7 T4 = 33	All patients had surgery, some had postop. RT, but not specified exactly.	16/92 (17%)	73/92 (79%)
Joosten et al [22]	2017	1990 - 2014	77	Only SCC	T1 = 21 T2 = 26 T3 =1 T4 = 29	Surgery only = 63 Surgery with postop. RT = 14	N/A	48/77 (62%)
Moratin et al [23]	2018	1999 - 2016	68	Only SCC	T1 = 24 T2 = 18 T3 = 5 T4 = 18 Lost* = 3	Surgery only = 23 Surgery with postop. RT = 35 Preop. (Ch)RT with Surgery = 10	8/68 (12%)	43/68 (63%)
Sun et al [24]	2019	2000 - 2012	137 (105*)	Only SCC	T1 = 20 T2 = 54 T3 = 23 T4 = 40	Surgery only = 93 Surgery with postop. RT = 12 *Excluded from further analysis = 32	15/105 (14%)	68/105 (65%)

Table 1: Continued.

First author	Publication year	Inclusion period	Sample size (n=)	Histological tumour type	T-stage of SCC-tumours	Treatment modalities of SCC tumours	5yr local recurrence rates	5yr overall survival outcomes
Hakim et al [25]	2019	1991 - 2018	77	Only SCC	Not specified	Surgery only = 51 Surgery with postop. RT = 20 RT only = 6	16/77 (21%)	47/77 (61%)
Slieker et al [2]	2019	2000 - 2015	95	Only SCC	T1-2 = 44 T3-4 = 51	Surgery only = 57 Surgery with postop. (Ch)RT = 38	N/A	61/95 (64%)
Oyhama et al [26]	2020	1999 - 2014	90	Only SCC	T1 = 15 T2 = 32 T3 = 13 T4 = 30	Surgery only = 42 Preop. RT with surgery = 3 Preop. intra-art (Ch)RT with surgery = 40 RT only = 5	N/A	74/90 (82%)
Slieker et al [27]	2020	2000 - 2015	95	Only SCC	T1-2 = 44 T3-4 = 51	Surgery only = 57 Surgery with postop. (Ch)RT = 38	23/95 (24%)	N/A

Table 2: Newcastle-Ottawa quality assessment results. In every category, each study could score either no points (/), or one point (*) and in some cases two points (**). The letters between parentheses correspond with the specific answers in the Newcastle-Ottawa Quality Assessment scale. For instance, in the column Selection - ascertainment of exposure, the (a) corresponds with 'secure record (e.g., surgical records)'. See Newcastle-Ottawa Quality Assessment Scale for more details.

Study (first author)	Selection - representativeness of the cases	Selection - selection of the non-exposed cohort	Selection - ascertainment of exposure	Selection - outcome not present at start study	Comparability of cases and controls based on design or analysis	Outcome - Assessment of outcome	Outcome - follow-up long enough for outcome?	Outcome - Adequacy of follow-up of cohorts	Total score (max. 9)
Binahmed	* (a)	* (a)	* (a)	*	*	* (b)	*	/ (d)	7
Dalal	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Eskander	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Feng	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Givi	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Hakim	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Joosten	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Koshkavera	* (a)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Meng	* (b)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Moratin	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Morice	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Oyhama	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Poeschl	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Ramalingam	* (b)	* (a)	* (a)	*	**	* (b)	*	* (a)	9
Slieker	* (a)	* (a)	* (a)	*	**	* (b)	*	* (b)	9
Slieker	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Sun	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Troeltzsch	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Wang	* (b)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8
Yang	* (a)	* (a)	* (a)	*	**	* (b)	*	/ (d)	8

Meta-analysis: LR rates

The results of the meta-analyses are presented in Table 3, column A. The forest plot is presented in Figure 2A. The primary outcome, '5-year LR rate', was extracted or synthesised from 14/20 studies. In total, 5-year LR was reported in 230/1168 patients. The reported 5-year LR rates varied between 9.0% - 46.8%. The pooled random-effects 5-year LR rate was 19.3% (range 15.1% - 23.9%). The LR rates have been stable throughout the years, except for one outlier [10].

Meta-analysis: OS rates

The results of the meta-analyses are presented in Table 3, column B. The forest plot is shown in Figure 2B. The outcome '5-year OS rate' was extracted or synthesised from 19/20 studies.

In total, 864/1499 patients survived after 5 years. The reported 5-year OS rates varied between 25% - 82.2%. The pooled random-effects 5-year OS rate was 53.7% (range 46.3% - 61.1%). The forest plot demonstrates that the 5-year OS rate was lower in 5 studies [9-11, 15, 20].

Subgroup analysis: surgery only vs surgery with (neo)adjuvant treatment

Four studies from which the 5-year OS rate per treatment group could be extracted or synthesised [13, 17, 26, 2/27]. However, one study did not specify their treatment protocol in any way and was consequently removed from the subgroup analysis [17].

In the remaining three studies [13, 26, 2/27], all patients were primarily treated with surgery only or surgery with (neo)adjuvant treatment.

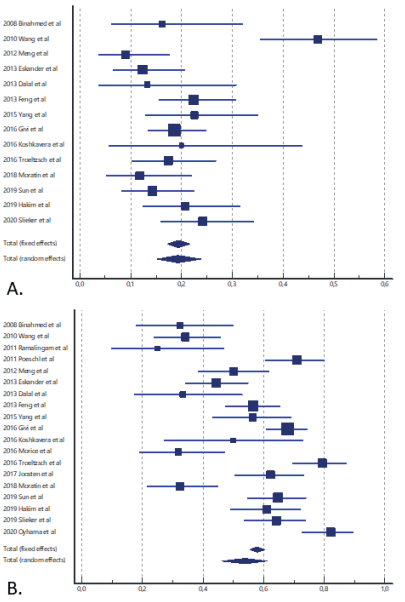
In case of advanced disease, close/positive surgical margins (after reresection), cervical lymph node involvement, extracapsular spread, unfavourable histopathological features [13, 26, 2/27] and involvement of soft palate/pterygoid process/pterygoid muscles [26], either postoperative radiotherapy [13], postoperative (chemo)radiotherapy [2/27] or preoperative intra-arterial chemoradiotherapy [26] was reported.

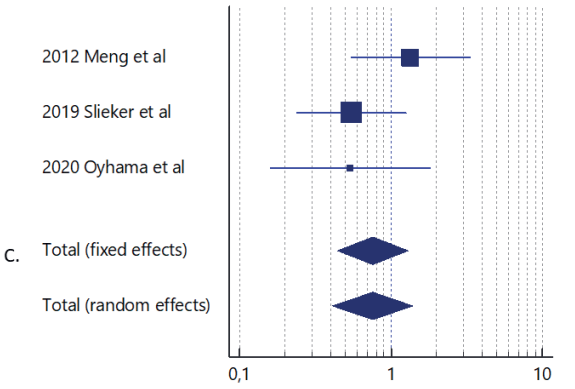
The results of the subgroup analysis are listed in Table 3, column C. The forest plot is displayed in Figure 2C. The pooled random-effects odds ratio (OR) on the 5-year OS rate between the two treatment groups was not statistically significant: OR .76 (95% CI .41 – 1.40).

Table 3: Pooled results of the meta-analyses on local recurrence (LR) (column A), overall survival (OS) (column B), and the subgroup analysis (column C).

A. 5-year local recurrence				B. 5-year overall survival				C. Subgroup analysis: 5-year overall survival per treatment group				
Study (first author)	**Total LR / SCC patients**	**LR rate (%)**	**95% CI**	**Study (first author)**	**Total alive/ SCC patients**	**OS rate (%)**	**95% CI**	**Study (first author)**	**Surgery + (neo)adjuvant treatment (total alive/total patients)**	**Surgery only (total alive/total patients)**	**Odds ratio**	**95% CI**
Binahmed et al	8/37	16.2%	6.2% - 32.0%	Binahmed et al	12/37	32.4%	18.0% - 49.8%	Meng et al	17/32	21/46	1.35	.55 – 3.34
Wang et al	37/79	46.8%	35.5% - 58.4%	Wang et al	27/79	34.2%	23.9% - 45.7%	Slieker et al	17/38	34/57	.55	.24 – 1.26
Meng et al	7/78	9.0%	3.7% - 17.6%	Ramalingam et al	6/24	25.0%	9.8% - 46.7%	Oyhama et al	32/40	37/42	.54	.16 – 1.82
Eskander et al	12/97	12.4%	6.6% - 20.6%	Poeschl et al	66/93	71.0%	60.6% - 79.9%					
Dalal et al	4/30	13.3%	3.8% - 30.7%	Meng et al	39/78	50.0%	38.5% - 61.5%					
Feng et al	29/129	22.5%	15.6% - 30.7%	Eskander et al	43/97	44.3%	34.2% - 54.8%					
Yang et al	14/62	22.6%	12.9% - 35.0%	Dalal et al	10/30	33.3%	17.3% - 52.8%					
Givi et al	37/199	18.6%	13.4% - 24.7%	Feng et al	73/129	56.6%	47.6% - 65.3%					
Koshkavera et al	4/20	20.0%	5.7% - 43.7%	Yang et al	35/62	56.5%	43.3% - 69.0%					
Troeltzsch et al	16/92	17.4%	10.3% - 26.7%	Givi et al	135/199	67.8%	60.9% - 74.3%					
Moratin et al	8/68	11.8%	5.2% - 21.9%	Koshkavera et al	10/20	50.0%	27.2% - 72.8%					
Sun et al	15/105	14.3%	8.2% - 22.5%	Morice et al	15/47	31.9%	19.1% - 47.1%					
Hakim et al	16/77	20.8%	12.4% - 31.5%	Troeltzsch et al	73/92	79.3%	69.6% - 87.1%					
Slieker et al	23/95	24.2%	16.0% - 34.1%	Joosten et al	48/77	62.3%	50.6% - 73.1%					
				Moratin et al	22/68	32.4%	21.5% - 44.8%					
				Sun et al	68/105	64.8%	54.8% - 73.8%					
				Hakim et al	47/77	61.0%	49.2% - 72.0%					
				Slieker et al	61/95	64.2%	53.7% - 73.8%					
				Oyhama et al	74/90	82.2%	72.7% - 89.5%					
Total (fixed effects)	230/1168	19.4%	17.1% - 21.7%	**Total (fixed effects)**	864/1499	57.8%	55.3% - 60.3%	**Total (fixed effects)**	66/110	92/145	.76	.44 – 1.30
Total (random effects)		19.3%	15.1% - 23.9%	**Total (random effects)**		53.7%	46.3% - 61.1%	**Total (random effects)**			.76	.41 – 1.40

Figure 2: Forest plots of the meta-analyses. A. Forest plot of 5-year LR rates: studies are listed on the y-axis. The x-axis is the LR rate (x100%). B. Forest plot of the 5-year OS rates: studies are listed on the y-axis. The x-axis is the OS rate (x100%). C. Subgroup analysis of treatment groups 'surgery only' vs 'surgery + (neo)adjuvant treatment: studies are listed on the y-axis. On the x-axis are the odds ratios (<1 favours the surgery group, >1 favours the (neo) adjuvant group).





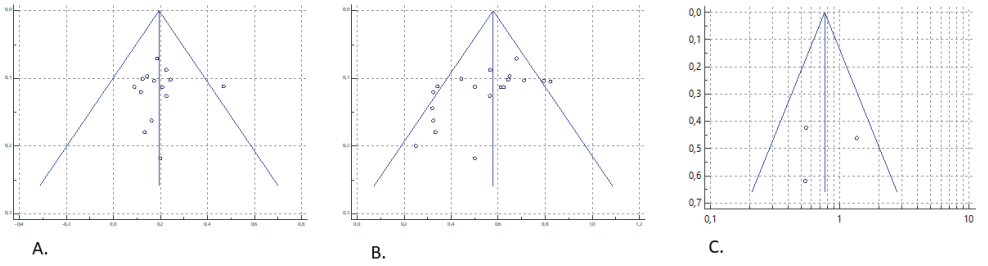
Funnel plots and heterogeneity tests

Funnel plots of the studies are presented in Figure 3. The funnel plot of the LR meta-analysis is symmetric, with one outlier [10]. Heterogeneity was substantial (I^2-index of 71.97%, $p \leq .0001$), but if the outlier [10] was removed from the analysis, heterogeneity was not significant (p=.20).

The funnel plot of the OS meta-analysis is asymmetrical. Heterogeneity was considerable (resp. I^2-indexes of 88.2%, $p \leq .0001$).

The funnel plot of the subgroup analysis of patients treated with surgery (with or without (neo)adjuvant treatment) was symmetrical. Heterogeneity was not significant (p=.29).

Figure 3: Funnel plots. A. Funnel plot of the meta-analysis on the 5-year LR rate. B. plot of the meta-analysis on the 5-year OS rate. C. Funnel plot of the subgroup analysis of treatment groups.



A. B. C.

Risk factors - LR

LR was significantly correlated with four risk factors (Table 4).

Positive surgical margins were significantly associated with LR in one study [12]. Patients with positive surgical margins were treated with adjuvant radiotherapy in this specific study [12]. However, two other studies had different treatment protocols. They found no statistical correlation with positive surgical margins [19, 27]: either the patients with positive surgical margins were treated with reresection if possible, and adjuvant (chemo)radiotherapy [27], or the patients were treated with adjuvant (chemo)radiotherapy [19].

Similarly, perineural invasion was significantly associated with LR in one study (p=.0423) [19], but this was not corroborated in another study (p=.599) [27]. The same was found for vascular invasion [19, 27]. Again, both studies had different treatment protocols. One applied adjuvant (chemo)radiotherapy [19, 27], but the other study also performed reresection in case both adverse tumour characteristics and positive surgical margins were present [27].

In addition, tumour location was correlated with LR in one study [21] but not in another study [23]. Both studies defined tumour location differently, either hard palate/maxillary alveolus [21] or molar and retromolar area [23].

Risk factors – OS

Various factors were correlated with OS (Table 4). Age [2, 20], advanced tumour stage (T3-4) [10, 17, 22, 24, 25] and positive surgical margins [2, 11-13, 17, 20, 25] were all correlated with decreased OS rates in multiple studies.

In addition, three histopathological tumour characteristics were correlated with decreased OS rates: large tumour volume [23], ulcerative tumour [23] and non-cohesive tumour growth [2]. However, these histopathological risk factors have not been verified in other studies.

Furthermore, posterior tumour location, defined as tumour involvement of the soft palate, infratemporal fossa, pterygoid muscles and pterygoid process, was correlated with decreased OS rates in multiple studies [10, 13, 26]. Moreover, tumour involvement of the nasal fossa, maxillary sinus and orbital floor was also correlated with decreased OS rates [20]. One

study demonstrated that significant postoperative midfacial defects are also associated with reduced OS rates [24].

Five studies reported that cervical lymph node involvement was correlated with decreased OS rates [2, 17, 20-22]. On the other hand, three studies found no significant correlation between cervical lymph node involvement and survival [13, 25, 26]:

In the first study, there were 46/78 (59%) patients with T1-2 tumours, and additionally, all patients with T3-4 tumours were deemed at high risk for regional failure and were therefore treated with neck dissections [13].

In the second study, 71/77 patients had a primary surgical resection, and a large proportion (59/71) of these patients had neck dissections, of which 22/59 were elective (12 T1, 10 T2) [25]. The third study used a standardised treatment

for late-stage T2 and T3-4 tumours, consisting of maxillary resection with neck dissection, neo-adjuvant intra-arterial chemotherapy, and cervical lymph node involvement adjuvant radiotherapy of the neck. Although in the univariate analysis, cervical lymph node involvement was significantly correlated with decreased OS rates (p=.015), cervical lymph node involvement was not significant in multivariate analysis (p=.076) [26].

Two studies specifically investigated elective neck dissection as a potential prognostic factor [16, 18]:

One study reported that elective neck dissection had significant survival benefits for patients with T2-T4 tumours (p=.048) [16]. The other study said that elective neck dissection was significantly correlated with lower regional recurrence rates (p=.031) and improved overall survival rates (p=.043).

Furthermore, one study noted that tumour recurrence was significantly correlated with lower rates of OS (p<.0005), although no significant difference between local or regional recurrence could be calculated (p=.778) [12].

The significant correlation between tumour recurrence and OS rate was corroborated in another study. However, this study analysed either LR (p<.01) separately or LR grouped with regional recurrence (p=.001) [17]. Moreover, two additional studies reported that local recurrence not surgically salvageable or requiring extensive salvage surgery was significantly correlated with decreased rates of OS [10, 27].

Lastly, patients with distant metastasis had significantly decreased OS rates (p=.04) [25].

Table 4: risk factors associated with MSCC. Risk factors associated with either local recurrence or mortality are listed per study with the accompanying p-values. Significant p-values are bold. Legend: N/A = not applicable.

	Binah-med	Wang	Ramalin-gam	Poeschl	Meng	Eskan-der	Dalal	Feng	Yang	Givi	Koshkavera	Morice	Troeltzsch	Joosten	Moratin	Sun	Hakim	Slieker	Oyhama	Slieker
Risk factors associated with local recurrence																				
Surgical margins	N/A	N/A	N/A	p<.0005	N/A	N/A	N/A	N/A	N/A	N/A	p=.7733	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.414
Perineural invasion	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p=.0423**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.599
Tumour location	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p≤.05**	N/A	p>.05	N/A	N/A	N/A	N/A	N/A
Vascular invasion	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.8177	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p=.003**
Risk factors associated with overall survival																				
Age	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	p=.20	**p=.007**	p=.785	N/A
Advanced T-stage (T3-4)	p=.056	**p=.0001**	N/A	p=.131	p=.73	N/A	N/A	N/A	**p<.036**	N/A	N/A	N/A	N/A	**p=.007**	p>.05	**P<.001**	**p<.02**	N/A	p=.607	N/A
Large tumour volume	N/A	**p=.001**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ulcerative tumour	N/A	**p=.0001**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Non-cohesive growth	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p<.015**	N/A	N/A
Involvement of nasal fossa, maxillary sinus or orbital floor	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Posterior tumour location	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	p=.841	N/A	N/A	p=.46	N/A	N/A	p>.05	N/A	N/A	N/A	**p=.031**	N/A
Involvement of infratemporal fossa and/or soft palate	N/A	**p=.017**	N/A	N/A	**p=.001**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cervical lymph node involvement	N/A	N/A	N/A	N/A	p>.57	N/A	N/A	N/A	**p=.018**	N/A	N/A	**p<.005**	**p<.03**	**p=.006**	N/A	N/A	p=.39	**p<.044**	p=.076	N/A
Elective neck dissection	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**P=.048**	N/A	**p=.043**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Distant metastasis	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p=.04**	N/A	N/A	N/A
Surgical margins	p>.05	p=.123	**p=.007**	**p<.0001**	**p=.001**	N/A	N/A	N/A	**p=.019**	N/A	N/A	p<.05	N/A	N/A	N/A	N/A	**p=.02**	**p<.053**	N/A	N/A
Large midfacial defects (Brown class IIc/IId/III)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p<.001**	N/A	N/A	N/A	N/A
Tumour recurrence (local and/ or regional)	N/A	N/A	N/A	**p<.0001**	N/A	N/A	N/A	N/A	**p=.002**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Local recurrence not surgically salvageable or requiring extensive salvage surgery	N/A	**p=.001**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	**p=.009**

Discussion

The first objective of this study was to analyse the 5-year LR and OS rates of MSCC.

The pooled 5-year LR rate was 19.3%. None of the reported 5-year LR rates was significantly different, except for one study [10]. The high LR rate in this study [10] might be partially explained by the large proportion of patients (30%) who had primary treatment with concurrent chemoradiotherapy. Also, a large proportion of their patients had positive/close margins (36%), which were subsequently treated with postoperative radiotherapy [10], which in turn is correlated with a higher risk of LR [12]. Treatment of positive/close margins by reresection and postoperative (chemo)radiotherapy might decrease the risk of LR because no statistical correlation with LR was found for these treatment protocols [19, 27].

The pooled 5-year OS rate was 53.7%. In most studies, the 5-year OS rates varied between 44% - 92%, except for 5 studies whose 5-year OS rates varied between 25% - 34.2% [9, 10, 11, 15, 20]. Two factors might explain the lower OS rates in these studies: a substantial proportion of cases with (chemo)radiotherapy as primary treatment [9, 10, 20] and a large proportion of cases with advanced tumour stages [10, 11, 15, 20].

Furthermore, elective neck dissection was also associated with improved 5-year OS rates [16, 18]. A recently published meta-analysis corroborates the beneficial effect of elective neck dissection on survival in MSCC patients [28].

What is more, the subgroup analysis of surgery vs surgery with (neo)adjuvant (chemo) radiotherapy resulted in non-significant OR .76 (.41 – 1.40) for patients in the (neo)adjuvant treatment group. These results mean that current (neo)adjuvant treatment protocols for adverse tumour characteristics successfully improve OS rates for MSCC patients. Curiously, the (neo)adjuvant treatment regimens were slightly different in all three studies of the subgroup analysis, but none were significantly better or worse [13, 26, 2/27]. Therefore, more research is warranted to ascertain which (neo)adjuvant treatment protocol is optimal for MSCC.

The second objective was to identify risk factors associated with LR and OS of MSCC.

There were only 5 studies that conducted risk factor analyses with regards to LR. The results were contradictory for all identified risk factors [12, 19, 21, 27]. Therefore, more research into risk factors for LR of MSCC is necessary to aid the physician in clinical decision-making. After all, local recurrence not surgically salvageable or requiring extensive salvage surgery was associated with decreased OS rates [2, 10].

Various OS-related risk factors identified for MSCC are similar to those previously identified for oral cancer in general (e.g., age, advanced tumour stage, surgical margins, cervical lymph node involvement, distant metastasis) [29].

One risk factor specific to MSCC was associated with lower rates of OS in multiple studies: posterior tumour extension defined as an extension into the soft palate, infratemporal fossa, pterygoid muscles and/or pterygoid process [10, 13, 26]. Additionally, tumour involvement of the nasal fossa, maxillary sinus and orbit was also associated with

decreased OS rate in one study [20]. Interestingly, tumour locations defined as dorsal to the premolar [17], dorsal to the first molar [20] and the (retro)molar area [23] were not significantly correlated with OS.

Although not oral cancer, similar correlations between tumour extension and overall survival were reported for sinonasal squamous cell carcinoma [30-32].

Although the quality assessment score of most studies was good, all studies were at risk of information bias because of their observational nature. The risk of information bias is most likely the result of the low incidence of MSCC. Most single-centre studies had small sample sizes, which they accumulated over many years. Just one of the included single-centre studies had a sample size larger than 150 cases [18]. This study had an inclusion period of 26 years, which means that patient volumes in hospitals are meagre. High patient volumes in specialised cancer centres are associated with better survival outcomes [33-35]. And so, for MSCC patients, higher patient volumes might benefit treatment outcomes and allow for higher-level research [36, 37].

One way to increase patient volumes might be to designate specific head and neck cancer centres as dedicated maxillary cancer centres with a dedicated maxillary cancer team.

Conclusion

Local recurrence rates were comparable across studies. More research into the risk-reduction of local recurrence is warranted. Surgical resection of the primary tumour with elective neck dissection improves survival. Postoperative radiotherapy, postoperative chemoradiotherapy and preoperative intra-arterial chemoradiotherapy all improve survival when adverse tumour characteristics are present. Finally, tumour extension into the soft palate, infratemporal fossa, pterygoid muscles and the pterygoid process is associated with lower survival in MSCC.

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Chapter 4

Oral Squamous Cell Carcinoma involving the Maxillae: Factors Affecting Local Recurrence and the Value of Salvage Treatment for Overall Survival

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Abstract

Objective: To determine factors associated with local recurrence (LR) of oral squamous cell carcinoma involving the maxillae (MSCC) and overall survival (OS) after salvage treatment.

Materials and Methods: Retrospective study of MSCC operated between 2000 and 2015. Kaplan-Meier survival and Cox regression were used for analysis of MSCC-associated clinical and histopathological factors.

Results: Ninety-five patients were included. LR occurred in 24% of patients. Vascular invasion significantly increased the risk of LR (hazard ratio 4.595, p= .003). Local salvage surgery, in the area of the original tumour, significantly prolonged OS, compared to palliative treatment (p= .001) and extensive salvage surgery (p= .013). Extensive salvage surgery, requiring resection of adjacent facial structures, did not prolong OS compared to palliative treatment (p= .186).

Conclusion: MSCC with vascular invasion has higher risk of LR. Salvage surgery may prolong OS in small recurrences but might have dubious value for larger recurrences infiltrating adjacent facial structures

Introduction

The preferred treatment for most malignant tumours involving the maxillae is surgery. The surgical approach and extent of the resection depend on the site and size of the tumour. Complete surgical removal of the tumour is critical as compromised margins impair the prognosis [1]. Surgical removal of maxilla tumours can be technically challenging because certain areas are difficult to access, and the visibility may be poor. At the same time, vital structures near the tumour should be preserved. Local recurrence (LR) after maxillectomy is in part due to the relative inaccessibility of cranial and dorsal margins. Knowledge of other risk factors may help to early detect LR.

There is no consensus on the optimal salvage treatment strategy for recurrent tumors involving the maxillae. Salvage surgery is often the treatment of choice, but it is frequently at the cost of morbidity and quality of life [2]. Insight into the overall survival rates of patients who have had salvage treatment of recurrent tumors involving the maxillae, might provide better information for physicians and patients, which may improve decision-making.

The aim of this study is to identify factors associated with increased risk of LR after surgical treatment of oral squamous cell carcinoma involving the maxillae (MSCC) and to identify factors associated with decreased overall survival (OS) of salvage treatment of locally recurrent MSCC.

Subjects and Methods

This study was granted an exemption from formal ethics review in writing by the 'Institutional Review Board Utrecht', because of its retrospective nature. Inclusion criteria were patients with MSCC, originating from the mucosa located on the alveolar process of the maxilla or the hard palate, operated between 2000 and 2015. Patients with second primary MSCC or sinonasal tumours were excluded.

Data collection

The following data was collected from medical records: date of birth, sex, alcohol and tobacco use, tumour location, tumour histology, type of surgery, operation date, pathological tumour stage, resection margins, spider growth pattern (non-cohesive growth), nerve invasion, vascular invasion, bone invasion, LR, date of LR diagnosis, location of LR, (extent of) salvage treatment, palliative treatment and date of death.

Preoperative screening

Preoperative screening consisted of physical examination, orthopantomogram, MRI-scan and/or CT-scan, chest X-ray, and ultrasound of the neck with fine needle aspiration cytology on indication. The 7th edition of the T/N/M-classification was used for staging [3]. All patients

were discussed in a weekly multidisciplinary team meeting and treated according to the national guidelines [4].

Surgery

Surgery was performed within 4 weeks from presentation in the outpatient department. Surgery included local excision, partial maxillectomy, hemi-maxillectomy or (sub)total maxillectomy. The surgical defects were managed with secondary wound healing, local flaps, free flaps or obturator prostheses.

Primary treatment of the neck

Patients with clinically positive lymph nodes were treated as a rule by neck dissection. A few patients received primary radiotherapy of the neck instead of neck dissection for patient-specific reasons.

Histology

The resection specimens were histologically examined. Data items included in the histopathology report of the resection specimen were: histological cell-type, tumour size, infiltration depth, resection margins (<1mm was considered positive [5]), spider growth pattern, nerve invasion, vascular invasion, and bone invasion. Data items included in the histopathology report of the neck dissection specimen were: number, size and site of metastatic lymph-nodes, and presence of extracapsular spread.

Adjuvant treatment for high risk factors

Positive surgical margins were managed by re-excision, if possible, preferably when the temporary obturator prostheses was adjusted after 2-3 weeks; if re-excision was not possible then postoperative radiotherapy was applied. Postoperative radiotherapy was also applied for extracapsular spread. Since 2005, chemotherapy was added to radiotherapy in patients <70 y with positive surgical margins and/or extracapsular spread without contraindications for chemotherapy.

Adjuvant treatment for intermediate risk factors

Postoperative radiotherapy was applied when three or more intermediate risk factors were present for recurrence, i.e., close resection margins, nerve invasion, pT3/T4 tumours, and/or multiple positive lymph nodes. Postoperative radiotherapy was started within 6 weeks of surgery [4].

Follow-up

Follow-up appointments were scheduled every 2 months in the first postoperative year, every 3 months in the 2nd year, every 4 months in the 3rd year, every 6 months in the 4th and 5th year. Patients free of disease after 5 years were discharged from follow-up.

Salvage treatment

Patients presenting with LR were considered for salvage surgery. Salvage surgery was classified as local salvage surgery when confined to the area of the original tumour. Salvage surgery was classified as extensive salvage surgery when requiring resection of adjacent facial structures (e.g., zygomatic resection, enucleation). Palliative treatment with (chemo) radiotherapy was offered for irresectable LR or when the patient declined surgery.

Definitions

The 5-year local control rate was defined as the proportion of patients without LR in the area of the original primary tumour within 5 years after surgery.

Analysis

The location of LR was listed to identify areas at risk for LR.

Kaplan-Meier survival analysis [6] was used to calculate the 5-year local control rate of MSCC. The log rank test (α=0.05) was conducted to analyse differences between groups.

Cox regression analysis was conducted to calculate whether clinical or histopathological factors were associated with the likelihood of 5-year LR.

Kaplan-Meier and Cox regression analyses were also used to analyse factors affecting OS after salvage treatment of locally recurrent tumours.

The following results of the regression analyses were listed: *p*-value, hazard ratios and 95% confidence intervals. Independent variables were considered statistically significant when $p<.05$. Missing data was handled by pairwise deletion.

Analysis was aided by the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS Inc., Chicago, USA) and guided by Laerd statistics [7].

Results

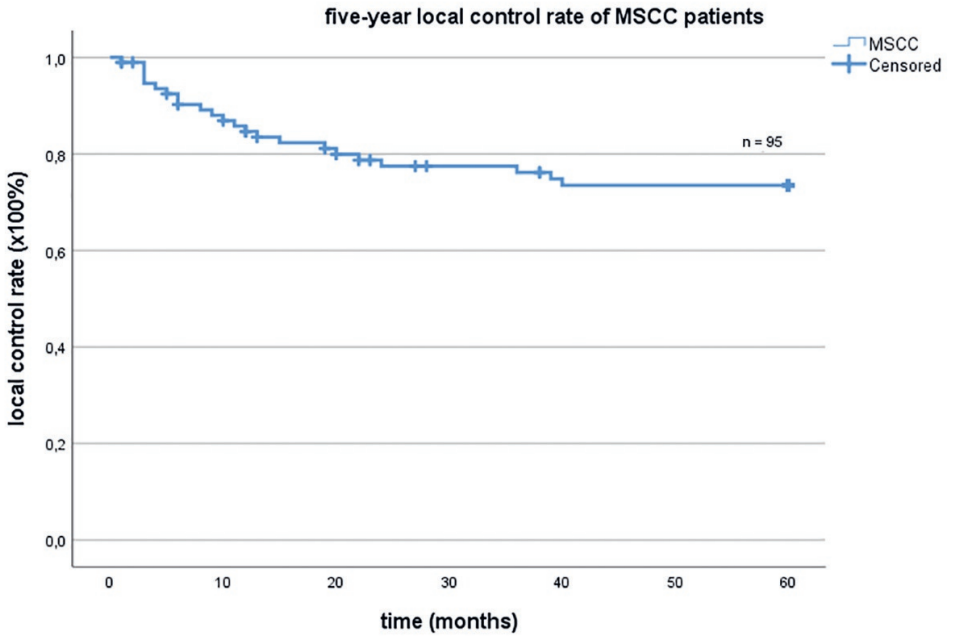
Between 2000 and 2015, 128 consecutive patients had been operated for malignant tumours of the maxilla. Of these 128 patients, 95 had MSCC tumours and were included. The patient characteristics are listed in Table 1.

Table 1: Pertinent clinical and histopathological data. Abbreviation: LR, local recurrence.

Patient characteristics	Total (n=95)
Sex	
male	41
female	54
Median age in years (lowest - highest)	
male	69 (46-93
female	71 (43–96)
Tumour location	
alveolar process	74
hard palate	21
cT-stage	
cT1-2	45
cT3-4	50
Treatment	
surgery	57
surgery +(chemo)radiotherapy	38
pT-stage	
pT1-2	44
pT3-4	51
Surgical margins	
clear (≥1 mm)	56
positive (<1 mm)	39
Bone invasion	
absent	34
present	61
Spider (non-cohesive) growth pattern	
absent	61
present	34
Nerve invasion	
absent	79
present	16
Vascular invasion	
absent	87
present	8
5-year LR	
disease free	72
locally recurrent disease	23

In total, 23 out of 95 (24%) patients developed LR. The mean time of diagnosis of LR was 12 months (range 1– 40 months) after primary treatment. At the 5-year endpoint, the local control rate of the MSCC group was 76% (Figure 1 for the Kaplan-Meier survival analysis).

Figure 1: Kaplan-Meier curve with five-year local control rate of MSCC patients. Abbreviation: MSCC, squamous cell carcinoma involving the maxillae.



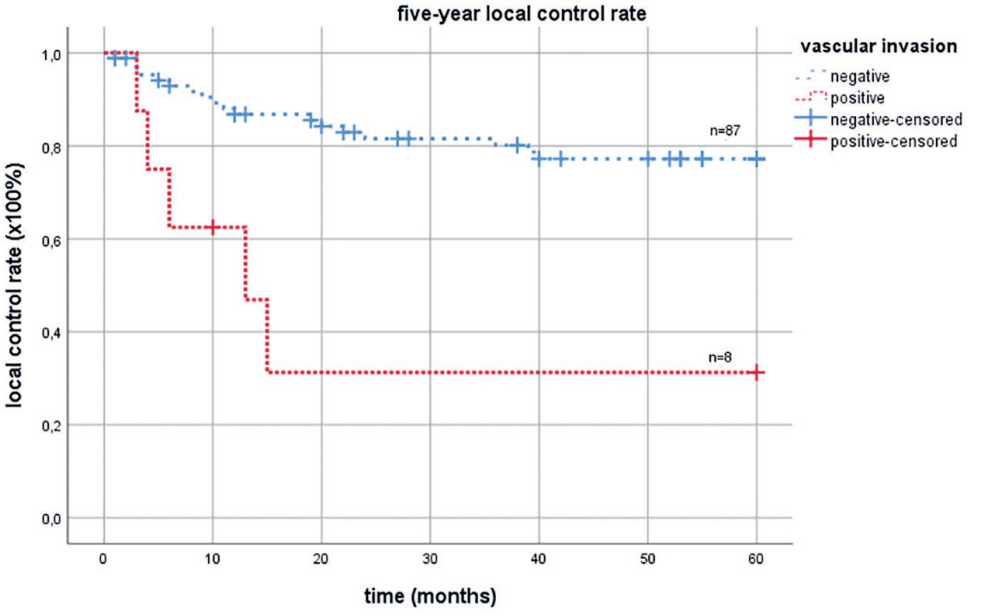
Factors associated with 5-year LR of MSCC

Cox regression analyses showed that vascular invasion (HR 4.595, 95% CI [1.683 – 12.543] *p*= .003) was significantly associated with the likelihood of LR within 5 years after surgery (Table 2). In this cohort, 6/8 patients with vascular invasion were diagnosed with LR within 15 months after surgery (Figure 2).

Table 2: Univariate Cox regression analyses of factors potentially associated with 5-year LR of MSCC.

Univariate Cox proportional hazard	*P*	Hazard ratio	Odds Ratio (95% CI)	
Sex	.399	.691	.293	1.630
Age	.248	1.021	.986	1.057
Tumour location	.548	.718	.244	2.113
cT-stage (T3-4 vs. T1-2)	.815	.907	.400	2.057
Treatment of primary tumour	.394	.680	.279	1.654
pT-stage (T3-4 vs. T1-2)	.289	1.574	.680	3.643
Surgical margins (positive vs. clear)	.414	1.412	.617	3.230
Bone invasion	.069	2.511	.930	6.780
Spider growth pattern	.872	1.073	.454	2.536
Nerve invasion	.599	1.336	.454	3.937
Vascular invasion	**.003**	4.595	1.683	12.543

Figure 2: Kaplan-Meier curve with 5-year local control rate of MSCC with vascular invasion vs. no vascular invasion.



Location of LR

In 17 out of 23 cases, LR emerged at the dorsal margin, either dorsocranial or dorsocaudal (Table 3). LR at dorsocranial margins extended into the maxillary sinus, nasal cavity, orbital complex, sphenoid bone, ethmoid bone, pterygoid process, and/or intracranially (carotid groove, meninges and subarachnoid space of frontal lobe). LR at the dorsocaudal margin extended into the soft palate, hypopharynx, retro- and parapharyngeal space or encased the internal carotid artery. In 4 out of 23 cases, LR was located at the lateral margin, involving the buccal mucosa. In 2 out of 23 cases, LR was located superficially at the mucosal surface of the resected primary tumour.

Table 3: Local recurrences: time to LR (months), site, compromised margin, type of salvage treatment, and survival time after salvage treatment.

Patient	Time to LR (months)	LR location	Compromised margins	Treatment of LR	Survival after salvage (months)
1	24	Left maxillary sinus, pterygopalatine fossa, buccal mucosa, orbit and ear	Dorsocranial	Palliative treatment	180
2	6	Orbit	Dorsocranial	Palliative treatment	4
3	8	Left maxillary sinus, infratemporal fossa, orbit and anterior subcutis	Dorsocranial	Palliative treatment	5
4	1	Right nasal cavity	Dorsocranial	Palliative treatment	1
5	3	Cavernous sinus, orbit, infra temporal fossa, sphenoid sinus and temporal lobe	Dorsocranial	Palliative treatment	5
6	3	Right zygomatic bone, orbit, palate and parapharyngeal space	Dorsocranial and dorsocaudal	Right enucleation and partial zygomatic resection	7
7	10	Left maxillary sinus, orbit, zygomatic bone, concha inferior and soft palate	Dorsocranial and -caudal	Right hemi maxillectomy, enucleation and zygomatic resection	11
8	4	Left buccal mucosa	Lateral	Palliative treatment	2
9	6	Right maxillary sinus, buccal mucosa, orbital surface and concha media	Dorsocranial and lateral	Enucleation, buccal resection and hemi rhinectomy	5
10	13	Upper left incisor, alveolar process and buccal mucosa	Lateral	Partial maxillectomy	16
11	15	Left retropharyngeal space, total encasement of left internal carotid artery	Dorsocaudal	Palliative treatment	3
12	3	Right soft palate	Dorsocaudal	Palliative treatment	2
13	5	Right maxillary sinus, nasal floor and retropharyngeal space	Dorsocranial and caudal	Palliative treatment	2
14	11	Retropharyngeal space, masticator space, carotid groove	Dorsocaudal	Palliative treatment	1
15	20	Right buccal mucosa	Lateral	Local resection	Alive after 36 months
16	22	Soft palate	Dorsocaudal	Local resection	11
17	19	Right buccal mucosa	Lateral	Local resection	Alive after 13 months
18	12	Dorsal maxillary bone invasion, buccal mucosa, mandible	Dorsocaudal	Palliative treatment	6
19	3	Left Eustachian tube	Dorsocranial	Local resection	Alive after 193 months
20	9	Medial hard palate	Local	Local resection	Alive after 30 months
21	36	Right hard palate	Local	Local resection	13
22	40	Right hard palate and maxillary tuberosity with invasion of maxillary sinus.	Dorsocranial	Partial maxillectomy	8
23	3	Right maxillary sinus	Dorsocranial	Palliative treatment	10

Overall survival after salvage treatment of recurrent MSCC

Cox regression analyses demonstrated that type of salvage treatment was significantly associated with the likelihood of OS after salvage treatment (p= .009) (Table 4). The presence of bone invasion (p= .056) and LR localisation (p= .083) approached a statistically significant association with the likelihood of OS. Previous treatment of the primary tumour, time interval to LR, surgical margins after salvage surgery, spider growth pattern, vascular invasion, perineural invasion of the recurrent tumour were not associated with the likelihood of OS after salvage treatment (all $p \geq .348$).

Table 4: Univariate Cox regression analyses of factors potentially associated with OS after salvage treatment of locally recurrent MSCC.

Univariate Cox proportional hazard	*P*	Hazard ratio	Odds Ratio (95% CI)	
Treatment of primary tumour	.327	1.613	.620	4.194
Time interval to LR (<6 months vs ≥6 months)	.348	1.556	.618	3.919
LR localisation	.083	-	-	-
Salvage treatment type	**.009**	-	-	-
Surgical margins after salvage (positive vs. clear)	.799	1.238	.238	6.430
Bone invasion	.056	10.634	.940	120.341
Spider growth pattern	.689	1.362	.299	6.198
Nerve invasion	.531	2.018	.225	18.114
Vascular invasion	.636	1.670	.200	13.934

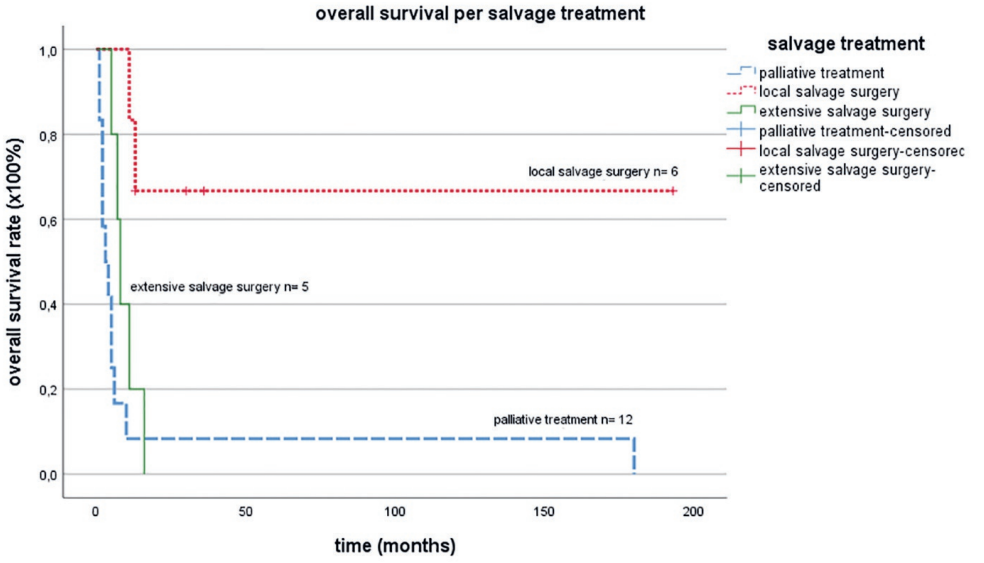
In this study, the salvage treatment types were classified as palliative treatment, local salvage surgery and extensive salvage surgery.

6 out of 23 LR-cases underwent local salvage surgery, 5 out of 23 LR-cases underwent extensive salvage surgery with resection of adjacent structures (orbit, ethmoid, zygoma, the other half of maxilla or external nose) and 12 out of 23 LR-cases received palliative treatment (Table 3).

The Kaplan-Meier survival analysis of these three salvage treatment groups is displayed in Figure 3. From the extensive salvage surgery group, 5 out of 5 patients (100%) died and from the palliative treatment group, 12 out of 12 patients (100%) died. Patients who received palliative treatment had a median survival time of 3.0 months (95% CI [0 – 6.4]), which was not significantly different (χ^2=1.753, p= .186) from the median survival time of patients who had extensive salvage surgery: 8.0 months (95% CI [5.8 – 10.1).

4 out of 6 patients (80%) from the local salvage surgery group were still alive at the time of this study. One deceased patient who had had local salvage surgery after 10 months, and the other died after 13 months. OS after local salvage surgery was significantly longer than OS after palliative treatment (χ^2=10.270, p= .001) and longer than OS after extensive salvage surgery (χ^2=6.174, p= .013).

Figure 3: Kaplan-Meier curves with overall survival rates after salvage treatment of recurrent MSCC.



Discussion

Vascular invasion was significantly associated with an increased likelihood of LR, even though there were only 8 patients with vascular invasion in this cohort. In the literature LR has been associated with positive surgical margins, T3-4 stage, dorsocranial tumour extension and nerve invasion [8-13], but to our knowledge not with vascular invasion.

LR occurred most frequently at the dorsal margins (cranial/caudal). A possible explanation for the occurrence of LR at the dorsal margins is the difficulty to achieve tumour free resection margins at these distant locations [14]. Another explanation for the occurrence of LR in the posterior region is that occult metastases may develop in the upper jugular nodes and/or lateral retropharyngeal nodes. These nodes are not routinely removed during the primary surgical treatment when they seem uninvolved during the preoperative screening, but they may develop occult metastasis [9, 15]. To reduce the risk of recurrent disease developing from these nodes, Tiwari et al. [9] and Yanamoto et al. [10] recommend en-bloc maxillectomy and internal dissection of the masticator space through a transmandibular approach.

Treatment of LR

To the best of our knowledge, this is the first study to analyse factors potentially associated with the likelihood of OS after salvage treatment. The type of salvage treatment was significantly associated with the likelihood of OS.

OS after local resection of recurrent tumours was longer than OS after palliative treatment or OS after extensive salvage surgery. Extensive salvage surgery had no survival

advantage over palliative treatment. Our results suggest that extensive salvage surgery should be considered with caution, as its value in terms of OS may be dubious. It should be considered that these extensive procedures may disturb the appearance and function while quality of life is particularly important in the final period of life.

Limitations

A limitation of this study was its retrospective study design. Risk of information bias is possible, because data was collected from medical records which were recorded by several physicians in a period of 18 years.

Furthermore, the 7th edition of the T/N/M-classification had to be used, because data on tumour infiltration depth was not retrievable for older cases, which made reclassification according to the 8th edition of T/N/M-classification unsuitable. Future studies about the effects of infiltration depth and T/N/M-classification differences of MSCC are therefore of interest.

Conclusion

LR occurred in 24% of patients. Patients with MSCC and vascular invasion are at risk for LR. Salvage surgery prolongs OS in case of small recurrences but might have dubious value regarding OS for larger recurrences infiltrating adjacent facial structures.

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Chapter 5

Predicting individualised mortality probabilities for patients with squamous cell carcinoma of the maxilla: novel models with clinical- and histopathological predictors

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Special thanks to Yannick R. Aerssens for constructing the webcalculator and Farahnaz Waissi for the statistical support.

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Abstract

Objective: to develop prediction models that calculate postoperative 2- and 5-year survival probabilities of patients with squamous cell carcinoma of the maxilla (MSCC).

Materials and methods: Data was collected from the medical records of patients who had been operated between 2000 and 2015 for MSCC. Potential clinical and histopathological predictors were identified. Confounding-(un)adjusted multivariate Cox and logistic regression models were computed with stepwise backward selection. Internal validation was performed to assess calibration and discriminatory ability.

Results: 95 patients with MSCC were included. 2-year follow-up was complete, but 10 patients had incomplete 5-year follow-up. Age, neck treatment, surgical margins, bone invasion, spindle growth, and vasoinvasive growth were associated with mortality. Models were adjusted for confounding with Charlson's comorbidities index. C-indexes were .841 and .770 respectively, and .838 and .749 after bootstrapping.

Conclusion: MSCC-specific mortality probability can be calculated with new prediction models.

Introduction

Squamous cell carcinoma of the maxilla (MSCC) is a relatively rare and distinct group of oral cavity cancers. The primary treatment is surgical resection of the maxillary tumour, and (chemo)radiotherapy of the neck if lymph nodes are involved [1], followed by prosthetic or surgical midfacial defect management [2]. The main factors that generally determine survival of MSCC are T-classification, N-classification, and local recurrence [1, 3, 4].

In addition, multiple other clinical, radiological and histopathological factors have been directly and indirectly associated with survival in oral cavity cancer [5, 6]. Moreover, having a multitude of these factors results in worse survival outcomes for patients [6]. For MSCC specifically thus far, these factors include posterosuperior tumour extension, perineural invasion, vasoinvasive growth, positive surgical margins and postoperative large midfacial defects [1, 4, 7-9].

Currently, the TNM classification system is the universally preferred method of tumour staging and is mainly based on anatomical tumour characteristics [10]. However, more outcome predictors have been identified over the years and prognostic shortcomings of the TNM classification have become more apparent [11]. The impact and interaction of multiple prognostic factors on outcome is still unclear and the uncertainty hinders the decision-making process. Reliable calculation of prognostic probabilities with prediction models may support physicians and patients in the decision-making process.

Today, clinical parameters and the TNM-classification have been incorporated into prognostic models that calculate personalized survival probabilities of head and neck cancer patients in general, and for specific patient-groups, like octogenarian patients and advanced larynx cancer patients [12-15]. One prediction model included specific imaging and clinical factors for head and neck cancer patients [16], and another even incorporated social factors to predict survival probabilities for oropharyngeal cancer patients [17]. However, there is no prediction model for MSCC specifically, nor are there prediction models that incorporated histopathological factors as predictive factors. Within the oral cancer subtypes, MSCC is a rare subtype with treatment strategies different from other oral cavity cancers. MSCC therefore deserves a specifically tailored prediction model [18].

The aim of this study is to develop prediction models that calculate 2- and 5-year mortality probabilities of MSCC-patients, with clinical- and histopathological predictors factors.

Materials and Methods

This retrospective study was approved by the local medical ethics research committee. The TRIPOD-checklist [19] was used as guideline for the development of the prediction models. Patients were eligible for inclusion if they presented with first primary MSCC, originating from mucosa or gingiva located on the hard palate or the upper alveolar process. Patients

with second primary MSCC or sinonasal tumours were excluded. The MSCC was confirmed by histopathological examination.

The departmental database was used to identify consecutive patients operated between 1 January 2000 and 31 December 2015 for MSCC.

Analysis was aided by the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS Inc., Chicago, USA)

Sample size calculation

An events per variable ratio of ≥10 is commonly recommended for regression analyses. Multiple studies have debunked the importance of this ratio however [20-25]. Rather, the number of predictors, selection of predictors, correlation among predictors, effect size, total sample size, event size and event fraction combined, all seem to determine whether regression analyses have adequate power [20-25]. It is therefore quite difficult to calculate the ideal sample size.

As a rule of thumb, the minimal sample size for a regression analysis is 50. For the analysis of multiple predictors, the following sample size formula is proposed: N = 50 +8*m*. *'m'* is the number of independent variables [26]. The number of predictors under consideration is 12. The sample size for multivariate models with five and six predictors is 90 and 98 patients, respectively.

Survival analysis

Kaplan Meier survival analysis of MSCC survival will be performed with censor at 5-years [27]. The median survival time was determined by interpolation.

Identification of new potential predictors

A literary search was conducted and the UMCU protocol for MSCC was reviewed to identify candidate predictors for multivariate analysis by two researchers (FJBS, EMVC).

The following predictors were analysed:

Clinical: sex, age, tumour location (alveolar process vs. hard palate), treatment primary tumour (surgery vs. surgery + (chemo)radiotherapy), neck treatment (surveillance vs. neck dissection/radiotherapy/sentinel node).

Histopathological: pT-classification (T1-2 vs. T3-4), pN-classification (pN0 vs. pN+), surgical margins (clear/close vs. positive), spindle growth, perineural invasion, vasoinvasive growth and bone invasion.

Multivariate analyses

Multivariate Logistic and Cox regression [27-29] was performed with stepwise backward selection of variables [30, 31]. Independent variables are eliminated from the backward stepwise regression according to Akaike's criterion (p >.157) [32]. Furthermore, to adjust the

prediction models to the confounding effect of the patient´s medical history and (lifestyle-related) comorbidities, Charlson's comorbidity index [33, 34] was scored for each patient and included as variable in the secondary analyses.

Patients were excluded/censored from logistic or Cox analyses if the 2- and/or 5-year follow-up was incomplete, or if data on confounding factors was missing.

To allow for easy calculation of 2- and 5-year overall mortality probabilities, the logistic regression models were tested and internally validated for the final prediction models.

Performance tests of logistic regression model

Statistical significance of the model was tested with the Omnibus Tests of Model Coefficients and considered significant if p<.05. The calibration of the prediction model was tested with the Hosmer and Lemeshow goodness of fit test [35, 36]. The prediction model was considered well calibrated when p>.05. Variance explained by the model was calculated with Nagelkerke's R^2.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated.

To calculate the discriminatory ability of the prediction model for different cut-off values, the C-index was calculated [36-38].

Internal validation of logistic regression model

To internally validate the discriminatory ability of the confounding-adjusted prediction models, average C-indexes were calculated for 100 bootstrapped resamples with replacement. [39]

To account for overfitting of the confounding-adjusted prediction models, shrinkage after estimation was performed by calculating the heuristic shrinkage estimator of van Houwelingen and le Cessie [40] and multiplying the prediction models with the shrinkage coefficient. If the prediction model did not meet the requirements, recalibration was not performed [41].

Logistic regression analyses resulted in logit equations that calculated log_odds [42] on the likelihood of two-year mortality. To calculate the probability of 2- and 5-year mortality, the logit equations were converted into probability equations and recalibrated with the shrinkage coefficient [43].

Webcalculator

The recalibrated probability equations were transformed into a user friendly webcalculator.

Missing data

Missing data was handled by pairwise deletion.

Results

In total, 95 patients with MSCC were included. Table 1 shows an overview of the clinical and histopathological characteristics of the included patients. Figure 1 shows the patient flow. The 2-year mortality rate was 27% and the 5-year mortality rate was 36%.

Survival analysis

The results of the Kaplan-Meier survival analysis are demonstrated in Figure 2. The group-specific median survival time was 19 months. The mean survival time was 45 months (40 – 49 months).

Figure 1: Patient flow after 2- and 5-years of follow-up.

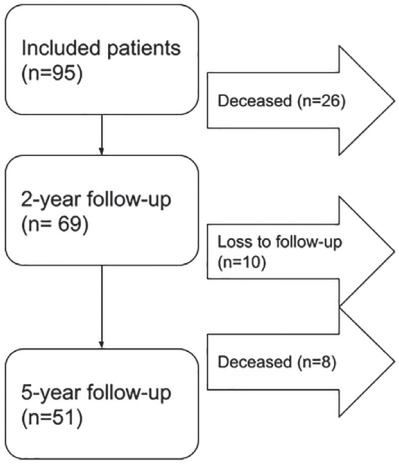

Figure 2: Kaplan-Meier 5-year survival analysis wit interpolation at group-specific median-survival time.

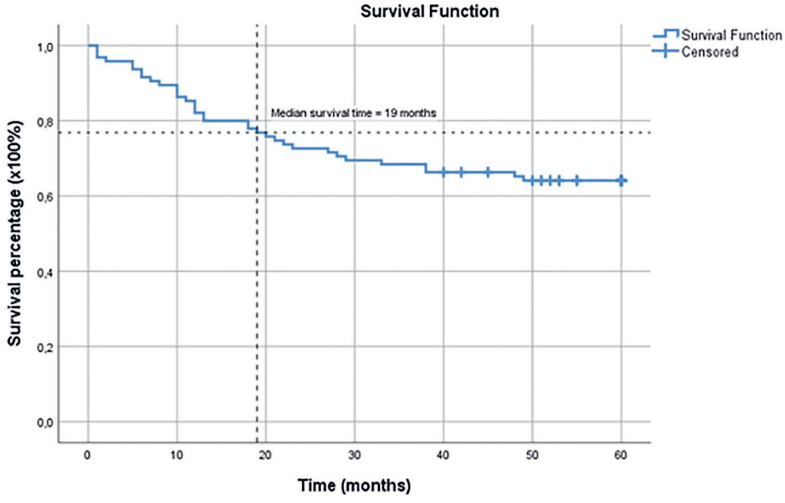

Table 1: Patient characteristics. Abbreviations: (C)RT, (chemo)radiotherapy, ND/RT, neck dissection/radiotherapy.

Patient characteristics	Baseline	2-year survivor group	2-year mortality group	5-year survivor group (10 censored)	5-year mortality group
		Potential predictors			
Total patients	95	69	26	51	34
Sex					
Male	41	30	11	26	13
Female	54	39	15	25	21
Age (median range)					
Male	69 (46-93)	-	-	-	-
Female	71 (43–96)	-	-	-	-
Tumour location					
Alveolar process	74	51	23	37	29
Hard palate	21	18	3	14	5
Treatment of primary tumour					
Surg	57	45	10	34	15
Surg + (C)RT	38	24	16	17	19
Neck management					
Surveillance	81	63	18	46	25
ND / RT	14	6	8	5	9
pT-stage					
pT1-2	44	37	7	25	10
pT3-4	51	32	19	26	24
pN-stage					
pN0	86	65	21	48	28
pN+	9	4	5	3	6
Surgical margins					
Clear/Close	56	47	9	35	14
Positive	39	22	17	16	20
Spindle growth					
Negative	61	51	10	41	16
Positive	34	18	14	10	18
Perineural invasion					
Negative	79	62	17	45	25
Positive	16	7	9	6	9
Vasoinvasive growth					
Negative	87	66	21	49	28
Positive	8	3	5	2	6
Bone invasion					
Negative	34	31	3	19	6
Positive	61	38	23	32	28
		Confounders			
Intoxication					
Tobacco / alcohol	60	46	14	14	19
No intoxication	34	22	12	12	15
Not reported (n=1)					
Comorbidity index					
1	4	4	0	3	0
2	12	8	4	6	5
3	12	10	2	8	3
4	25	18	7	12	10
5	16	12	4	10	4
6	16	10	6	7	8
7	7	5	2	4	3
8	0	0	0	0	0
9	3	2	1	1	1

Multivariate logistic and Cox analyses on 2- and 5-year mortality probability

The results of the multivariate logistic and Cox regression analyses with backward stepwise selection on 2- and 5-year mortality are reported in Table 2.

For 2-year mortality, 95 cases entered logistic and Cox analyses. The following predictors were significantly associated (p<.157): age (OR 1.094, HR 1.068), neck treatment (OR 6.714, HR 2.985), surgical margins (OR 3.452, HR 2.467), bone invasion (OR 7.351, HR 3.803), spindle growth (OR 5.491, HR 2.315) and vasoinvasive growth (OR 6.243, HR 3.673).

For 5-year mortality, 85 cases entered the logistic regression analysis (10 cases were censored due to incomplete follow-up) and 95 cases entered the Cox regression analysis. The following predictors were significantly associated with 5-year mortality: age (OR 1.083, HR 1.063), neck treatment (OR 4.540, HR 3.035), surgical margins (OR 3.600, HR 2.140), spindle growth (OR 4.452, HR 2.027) and vasoinvasive growth (OR 6.906, HR 4.090). Bone invasion was significantly associated with the 5-year mortality probability in the Cox regression analysis (HR 2.543), but not in logistic regression analysis.

Table 2: Results of the logistic and Cox regression analyses on the 2- and 5-year mortality probability unadjusted for confounding.

Logistic regression	β	SE	Wald	df	p	Odds ratio	95% CI for Odds Ratio		Cox regression	β	SE	Wald	df	p	Odds ratio	95% CI for Odds Ratio	
							Lower	Upper								Lower	Upper
2-year mortality																	
Age	.090	.035	6.604	1	.010	1.094	1.021	1.171	**Age**	.066	.023	8.455	1	.004	1.068	1.022	1.117
Neck treatment	1.904	.783	5.912	1	.015	6.714	1.447	31.161	**Neck treatment**	1.094	.481	5.162	1	.023	2.985	1.162	7.667
Surgical margins	1.239	.631	3.855	1	.050	3.452	1.002	11.889	**Surgical margins**	.903	.437	4.268	1	.039	2.467	1.047	5.811
Bone invasion	1.995	.892	5.001	1	.025	7.351	1.280	42.230	**Bone invasion**	1.336	.663	4.061	1	.044	3.803	1.037	13.941
Spindle growth	1.703	.629	7.332	1	.007	5.491	1.601	18.837	**Spindle growth**	.840	.432	3.785	1	.052	2.315	.994	5.394
Vasoinvasive growth	1.831	.950	3.716	1	.054	6.243	.970	40.184	**Vasoinvasive growth**	1.301	.543	5.748	1	.017	3.673	1.268	10.638
Constant	-10.938	3.190	11.760	1	.001	.000	-	-									
5-year mortality																	
Age	.080	.030	7.264	1	.007	1.083	1.022	1.148	**Age**	.061	.020	9.605	1	.002	1.063	1.023	1.104
Neck treatment	1.513	.707	4.582	1	.032	4.540	1.136	18.138	**Neck treatment**	1.110	.438	6.430	1	.011	3.035	1.287	7.158
Surgical margins	1.281	.568	5.081	1	.024	3.600	1.182	10.967	**Surgical margins**	.761	.372	4.186	1	.041	2.140	1.032	4.434
Spindle growth	1.493	.581	6.618	1	.010	4.452	1.427	13.890	**Bone invasion**	.933	.504	3.434	1	.064	2.543	.948	6.822
Vasoinvasive growth	1.932	1.007	3.681	1	.055	6.906	.959	49.723	**Spindle growth**	.706	.369	3.657	1	.056	2.027	.983	4.181
Constant	-7.655	2.368	10.451	1	.001	.000	-	-	**Vasoinvasive growth**	1.409	.494	8.143	1	.004	4.090	1.554	10.761

Multivariate logistic and Cox analyses adjusted for confounding

To adjust for the confounding effect of the patient's medical history and (lifestyle-related) comorbidities, the multivariate analyses were run, with the Charlson's comorbidity index added as a variable, while age was omitted as a predictor, because age is incorporated in Charlson's comorbidity index.

The results of the multivariate logistic and Cox regression analyses on 2- and 5-year mortality adjusted for confounding are listed in Table 3. The following predictors were significantly associated with 2-year mortality: neck treatment (OR 5.284, HR 2.246), surgical margins (OR 2.740, HR 2.075), bone invasion (OR 3.701, HR 2.697), spindle growth (OR 4.481, HR 2.402), vasoinvasive growth (OR 4.756, HR 2.762).

The following predictors were significantly associated with 5-year mortality: neck treatment (OR 3.954, HR 2.678), surgical margins (OR 2.709, HR 2.290), spindle growth (OR 3.694, HR 1.982), vasoinvasive growth (OR 5.099, HR 3.525).

Performance tests logistic regression

The results of the performance tests for both the 2-year- and 5-year mortality prediction models are listed in Table 4. All models had statistically significant predictive capability and good fit. Statistical variance varied between 30.5-48.4%. Diagnostic accuracy was >76% for all models. The respective sensitivity, specificity, PPV and NPV results for the adjusted 2-year model were 61.5%, 87.0%, 64.0%, 85.7%, and for the adjusted 5-year model were 58.8%, 88.2%, 76.9%, 76.3%.

Internal validation

The C-indexes for the adjusted 2-year and 5-year mortality models were .841 and .770, after bootstrapping the average C-indexes were .838 and .749 respectively.

The shrinkage coefficient of both the adjusted 2-year and 5-year mortality models were .805 and .770 respectively. The probability equations for the adjusted models were computed and recalibrated.

Webcalculator

The webcalculator can be accessed via mscc.oncologyheadneck.com or via the QR code:

Table 3: Results of logistic and Cox multivariate regression analyses on the 2- and 5-year mortality probability adjusted for confounding.

Logistic regression	β	SE	Wald	df	p	Odds ratio	95% CI for Odds Ratio		Cox regression	β	SE	Wald	df	p	Odds ratio	95% CI for Odds Ratio	
							Lower	Upper								Lower	Upper
2-year mortality																	
Neck treatment	1.665	.745	4.996	1	.025	5.284	1.227	22.748	**Neck treatment**	.809	.449	3.244	1	.072	2.246	.931	5.415
Surgical margins	1.008	.598	2.839	1	.092	2.740	.848	8.848	**Surgical margins**	.730	.439	2.768	1	.096	2.075	.878	4.901
Bone invasion	1.309	.766	2.922	1	.087	3.701	.825	16.595	**Bone invasion**	.992	.662	2.244	1	.134	2.697	.736	9.874
Spindle growth	1.500	.571	6.909	1	.009	4.481	1.464	13.710	**Spindle growth**	.876	.421	4.325	1	.038	2.402	1.052	5.487
Vasoinvasive growth	1.559	.880	3.140	1	.076	4.756	.848	26.684	**Vasoinvasive growth**	1.016	.518	3.841	1	.050	2.762	1.000	7.630
Constant	-4.008	1.143	12.289	1	.000	.018	-	-									
Comorbidity index	.099	.174	.326	1	.568	1.104	.786	1.552	**Comorbidity index**	.091	.104	.768	1	.381	1.095	.894	1.342
5-year mortality																	
Neck treatment	1.375	.683	4.057	1	.044	3.954	1.038	15.066	**Neck treatment**	.985	.402	6.006	1	.014	2.678	1.218	5.887
Surgical margins	.996	.516	3.734	1	.053	2.709	.986	7.442	**Surgical margins**	.829	.361	5.264	1	.022	2.290	1.128	4.648
Spindle growth	1.307	.535	5.972	1	.015	3.694	1.295	10.533	**Spindle growth**	.684	.361	3.599	1	.058	1.982	.978	4.019
Vasoinvasive growth	1.629	.935	3.033	1	.082	5.099	.815	31.898	**Vasoinvasive growth**	1.260	.470	7.173	1	.007	3.525	1.402	8.863
Constant	-2.108	.821	6.588	1	.010	.121	-	-									
Comorbidity index	.093	.156	.356	1	.551	1.098	.808	1.490	**Comorbidity index**	.102	.093	1.212	1	.271	1.108	.923	1.329

Table 4: Performance tests of each prediction model. Note: models were significant if Omnibus test p<.05. Models had good fit if Hosmer and Lemeshow p>.05. Sensitivity, specificity, PPV, NPV and accuracy calculated with cut-off value of .5. The C-indexes of every model and the bootstrapped C-indexes for the adjusted models were calculated.

	Omnibus Tests of Model Coefficients	Hosmer and Lemeshow test	Variance Nagelkerke's R2 (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	C-index	C-index bootstrap
2-year mortality unadjusted	$X^2(6)$ =38.620, p<.0001	$X^2(7)$ =5.462, p=.604	48.4%	57.7%	92.8%	75.0%	85.3%	83.2%	.861	-
2-year mortality adjusted	$X^2(6)$ =30.851, p<.0001	$X^2(7)$ =1.261, p=.989	40.1%	61.5%	87.0%	64.0%	85.7%	80.0%	.841	.838
5-year mortality unadjusted	$X^2(6)$ =30.869, p<.0001	$X^2(7)$ =8.64, p=.302	41.2%	64.7%	84.3%	73.3%	78.2%	76.5%	.814	-
5-year mortality adjusted	$X^2(5)$ =21.698, p=.001	$X^2(7)$ =4.317, p=.743	30.5%	58.8%	88.2%	76.9%	76.3%	76.5%	.770	.749

Discussion

In this study, multiple statistically significant multivariate prediction models were successfully computed, to calculate 2- and 5-year mortality probabilities with clinical- and histopathological predictors. The prediction models were statistically adjusted for the confounding effect of medical history and (lifestyle-related) comorbidities with Charlson's comorbidity index [33]. Both adjusted prediction models had good to moderate (bootstrapped) C-indexes and were recalibrated with the heuristic shrinkage factor [36-41].

The risk of selection bias and confounding was minimalized by the selective inclusion of MSCC and the exclusion of other oral cavity cancers. By employing stepwise backward regression with Akaike's criterion (p<.157) [32] during automated statistical predictor selection, the risk of selection bias was further reduced. In the future, the same method of developing this prediction model can be used to develop prediction models for other subgroups of oral cavity cancer and head and neck cancer.

Furthermore, this analysis included well-known histopathological factors, which are part of standard analysis in UMCU. These factors were strongly correlated with the mortality probability. So far, other prediction models have not included histopathological factors [12-17]. Based on our findings, these histopathological predictors should be considered for the development of future prediction models for other subgroups of oral cavity and head and neck cancer.

Both HR's and OR's were calculated with Cox and logistic regression, to facilitate broad interpretation of the predictive effects on the mortality probabilities.

In total, 10 patients had incomplete follow-up at 5-years and were deleted pair-wise from the logistic regression analyses of 5-year mortality. Bone invasion was significantly associated with 5-year mortality probability in Cox, but not logistic regression. Once these patients have completed their 5-year follow-up, the logistic 5-year mortality analysis can be revaluated. Although, the confounder-adjusted logistic models were internally validated and

recalibrated with bootstrapping, the performance should be tested and externally validated in another sample.

The probability equations used in the webcalculator, were constructed from the confounding-adjusted logistic regression analysis results, because they are user-friendly and easy to interpret.

Preoperatively, some histopathological factors are not yet knowable. However, the effects of (in)complete resection of the primary tumour, potential necessity for neck treatment and Charlson's comorbidity index [33] on the 2- and 5-year mortality probability may provide valuable preoperative insight into the patient's prognosis.

Postoperatively, the prognosis can be updated further by the addition of potential histological predictors. These prediction models might therefore aid physicians and patients with decision-making for treatment strategies and for the organisation and intensity of follow-up and (salvage) treatment planning. For instance, with knowledge of high mortality probability, these patients might benefit from more extensive screening for locoregional disease recurrence during follow-up.

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Chapter 6

Management of patients with midfacial defects after maxillectomy: a national e-survey on clinical practice

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Submitted

Abstract

Objectives: to acquire an overview of the current treatments of midfacial defects after maxillectomy in the Netherlands.

Methods: medical specialists from all 14 dedicated Dutch head and neck centres were invited to participate in an e-survey with 18 questions about midfacial defect management, obturator prosthetics, surgical reconstruction, hospital stay and follow-up. The e-survey was developed and tested by the research team before sending out.

Results: 26 participants were invited and 20 (77%) surveys were completed by 11 maxillofacial surgeons and 9 otolaryngologists from 12 hospitals in Alkmaar, Amsterdam, Den Haag, Enschede, Groningen, Leiden, Maastricht, Nijmegen, Rotterdam and Utrecht. Most participants favoured both obturator prosthetics and surgical reconstruction (70%), but some opted for only obturator prosthetics (15%). A wide variety of reconstructive procedures are performed, but 'pedicled flaps' for Brown I (91%) and 'fibular composite free-flap' for Brown II – VI (50 – 92%) were favoured. Length of stay (2 – 15 days) and follow-up consultations varied considerably across different hospitals (4 – 12 during the first year, 3 – 6 the second year and 2 – 4 the third year).

Conclusion: This study provides an overview of the management of midfacial defects after maxillectomy in the Netherlands and shows that management methods vary considerably.

Introduction

Oral squamous cell carcinoma (OSCC) is a rare disease. A small proportion of OSCC is located in the upper jaw or hard palate [1]. The first-choice treatment is surgery, with the aim to completely remove the tumour [2]. The extent of the resection determines the size of the subsequent midfacial defect. Midfacial defects can be classified in various ways. The Brown classification is frequently used and classifies the midfacial defect, based on the loss of horizontal and vertical components [3].

If the postoperative midfacial defect is not managed properly, the loss of orofacial function and cosmetic mutilation may lead to severe loss of health-related quality of life [4]. Nasal regurgitation through the defect, problems with mastication, impaired speech and upper airway infections are commonly reported problems.

The midfacial defect can be managed by the placement of an obturator prosthesis, or by surgical reconstruction with pedicled flaps or vascularized free-flaps.

Obturator prostheses are frequently associated with discomfort, leakage, complicated hygienic maintenance and need regular modifications [5-7]. Recent developments however, in particular 3D-planning, implant-support and/or frame reconstruction have greatly improved the fit and function of obturator prostheses [8]. Placement of an obturator prosthesis has many advantages. It requires no surgery, it is a quick method to manage the defect, relatively cheap, and allows for physical examination of the resection defect/ cavity during follow-up.

Various types of pedicled and vascularised free-flap reconstructive procedures for maxillary defects have been described. For instance, maxillary defects have been reconstructed by using temporalis pedicled flaps [9, 10], iliac crest and internal oblique muscle free-flaps [11], rectus abdominis soft tissue free-flaps [12, 13], latissimus dorsi soft tissue free-flaps [14], fibular composite free-flaps [15] and radial forearm soft tissue/composite free-flaps [14, 16]. It has not been established which reconstruction provides the best outcome for different midfacial defects. Therefore, it might seem that the choice is a matter of personal preference for both patient and surgeon.

The aim of this survey study is to acquire an overview of the current management of midfacial defects, prosthetically or surgically, by all centers of the Dutch Head and Neck Society (NWHHT). Medical specialists from these dedicated centres were invited to participate in the survey with questions about midfacial defect classification, obturator prosthetics, surgical reconstruction, types of surgical reconstruction per class, length of hospital stay and follow-up.

Methods

The CHERRIES-checklist [17] was used as a guide to report this study.

Approval and informed consent

Because this study did not involve any patients and/or patient data, consideration and approval by an IRB was not applicable.

Design

For this survey, the target population included otolaryngologists and oral maxillofacial surgeons from all dedicated oncological head and neck cancer centres from the Netherlands.

The target population was asked to participate via e-mail with a standard message. In the e-mail, information about the purpose of the survey, the approximate length of the survey and the names of the investigators were shared. No additional personal information was collected or stored for this survey.

Development and testing

The questions in this survey were formulated by the investigators. The final list of questions was drafted after discussion between the investigators until consensus was reached. The electronic survey was developed with Google Forms by one of the investigators (FJBS). The final questionnaire was subsequently incorporated into the electronic survey. The survey was pre-tested by the other investigators (EMVC, RdB), glitches were solved and questions reframed in case of unexpected interpretation. Finally, unique links to the electronic survey were generated.

Recruitment and access

This closed survey was shared with potential participants from the target population who were selected by the investigators (EMVC, RdB). Initial contact was made via e-mail with a standard message. A reminder was sent to participants after 2-3 weeks in case of no response. No additional announcements or advertisements were used to promote participation in the survey. No incentive was offered to provide answers to the survey questions.

Survey administration

The participants were asked to complete the survey between September of 2018 and January 2019. All participants received the same questionnaire, without randomization of the question order. Adaptive questioning was used to reduce unnecessary length and complexity of the questionnaire. The questionnaire contained 18 questions regarding the following topics: midfacial defect management, obturator prosthetics, 3D planning, surgical reconstruction, length of hospital stay, follow-up and follow-up diagnostics. There were 1-6 questions per topic.

The participants had the opportunity to review and change their answers. For some questions, the option 'not applicable' was present if applicable.

All responses to the survey were automatically entered into an electronic database.

Response rate

The completion rate was calculated by dividing the number of completed surveys by the total number of contacted participants. The total number of potential participants was predetermined by the investigators (EMVC, RdB), so no additional registration techniques were necessary.

Prevention of double entries

To prevent double entries, each user had to provide his/her e-mail address. When the survey was completed, both the e-mail address and the date and time of completion were registered in the database. In case double entries were present, the participant was contacted, so that the participant could choose which entry would be kept for analysis. If the participant was not available, then the most recent entry was used. No cookies or IP addresses were used to assign unique user identifiers.

Analysis

All of the questionnaires were included in the analysis. Sum totals, percentages, means, medial and ranges for the related questions were calculated in analyses. Graphs were plotted to visualize certain results. No additional weighting of items or propensity scores were used to adjust the results of the analysis.

Results

In total, 26 survey-invitations were sent to otolaryngologists and maxillofacial surgeons who were affiliated with head and neck oncological centres in the Netherlands. Twenty (77%) surveys were completed by 11 maxillofacial surgeons and 9 otolaryngologists from 12 hospitals in Alkmaar, Amsterdam, Den Haag, Enschede, Groningen, Leiden, Maastricht, Nijmegen, Rotterdam and Utrecht.

Midfacial defect management

In response to the question: "how are midfacial defects managed in case primary closure is not possible?", 14 participants (70%) answered that midfacial defects could be managed with both maxillary obturator prosthetics and surgical reconstruction. Three participants (15%) treat midfacial defects with obturator prosthetics only. Lastly, three otolaryngologists (15%) answered that midfacial defect management is referred to either oral and maxillofacial surgeons, or plastic surgeons in their respective hospitals.

Obturator prosthetics

In response to the question: "what kind of obturator prosthetics are generally used?", 14/17 (70%) of participants answered that both 'obturator prostheses' and 'obturator prostheses with implants' are used in their respective hospitals. Lastly, 13/17 (65%) participants also use 'obturator prostheses with frame reconstruction' in their hospitals.

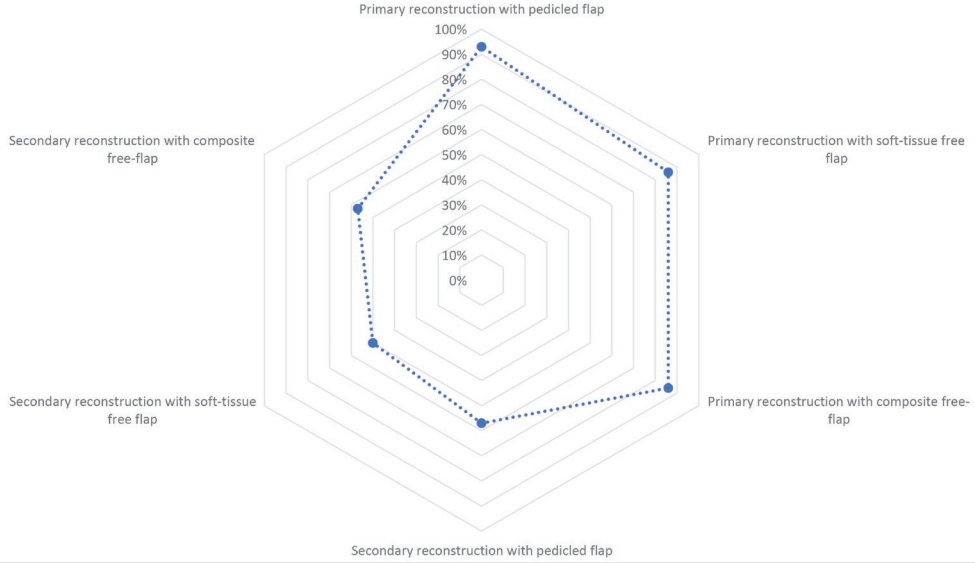
3D planning

In response to the question: "Does one utilise 3D for preoperative planning of surgical reconstruction of midfacial defects?", 13/14 (93%) of the participants answered positively.

Surgical reconstruction

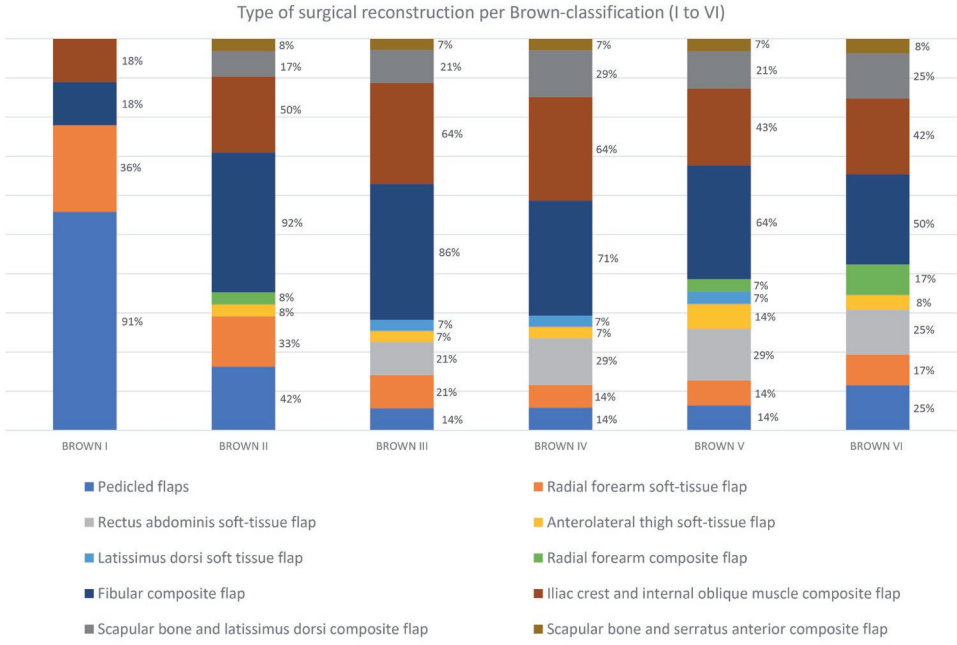
In response to the question: "What methods are used to treat midfacial defects with surgical reconstruction?", primary reconstruction with pedicled flaps (13/14 participants, 93%), soft tissue free-flaps (12 participants, 86%) and composite free-flaps (12 participants, 86%) were favoured, compared to secondary reconstruction with pedicled flaps (8 participants, 57%), soft tissue free-flaps (7 participants, 50%) and composite free-flaps (8 participants, 57%) (Figure 1).

Figure 1: Preferred types of surgical reconstruction.



In response to the question: "Which surgical reconstruction procedures are used per midfacial defect class of the Brown classification?" [18], participants could choose multiple procedures for all six Brown classes of midfacial defects. The results are displayed in Figure 2.

Figure 2: Preferred surgical procedures per Brown class (I – VI).



For Brown I: maxillectomy not causing an oronasal fistula, 'pedicled flaps' were chosen by 10/11 participants (91%), 'radial forearm soft-tissue free flaps' by 4 participants (36%) and both 'fibular composite free-flap' and 'iliac crest and internal oblique muscle free flap' were chosen by two participants (18%). Two participants noted that they would treat Brown I with an obturator prosthesis, not with surgical reconstruction. One participant had not responded to this question.

For Brown II: maxillectomy not involving the orbit, 11/12 participants (92%) had chosen 'fibular composite free-flap', 6/12 participants (50%) had the 'iliac crest and internal oblique muscle free flap', 5/12 participants (42%) had the 'pedicled flaps' and 4/12 (33%) had the 'radial forearm soft tissue free flap'. Various other reconstructive procedures were named by 1-2 participants (8 – 17%), see Figure 2. Two participants noted that they would treat Brown II with an obturator prosthesis, not with surgical reconstruction.

For Brown III: maxillectomy involving the orbital adnexae with orbital retention, 'fibular composite free-flap' was chosen by 12/14 participants (86%) and 'iliac crest and internal oblique muscle free-flap' was chosen by 9/14 participants (64%). Various other reconstructive procedures were named by 1-3 participants (7 – 21%), see Figure 2.

For Brown IV: maxillectomy with orbital enucleation or exenteration, 'fibular composite free-flap' was chosen by 10/14 participants (71%) and 'iliac crest and internal oblique muscle free-flap' was chosen by 9/14 participants (64%). Both the 'rectus abdominis soft tissue free-flap' and the 'scapular bone and latissimus dorsi composite free-flap' were chosen by 4 participants (29%). Various other reconstructive procedures were named by 1-2 participants (7-14%), see Figure 2.

For Brown V: orbitomaxillary defect, 9/14 participants (64%) had chosen 'fibular composite free-flap', 6 participants (43%) had chosen 'iliac crest and internal oblique muscle free-flap' and 4 participants (29%) had chosen 'rectus abdominis soft tissue free-flap'. Various other reconstructive procedures were named by 1-3 participants (7 – 21%), see Figure 2.

For Brown VI: nasomaxillary defect, 6/12 participants (50%) had chosen 'fibular composite free-flap' and 5/12 participants (42%) had chosen 'iliac crest and internal oblique muscle free-flap'. Various other reconstructive procedures were named by 1-3 participants (8-25%), see Figure 2. Two participants had not responded to this question.

Length of stay

In response to the question: "What is the average length of hospital stay (days) following a maxillectomy?", the length of stay varied between 2 – 15 days according to 17/20 participants. The average length of stay was 7.5 days.

Follow-up

In response to the question: "How many follow-up appointments are scheduled for maxillectomy-patients during the first, second and third year after the maxillectomy?", the range of consultations varied between 4 – 12 during the first year, 3 – 6 during the second year and 2 – 4 during the third year of follow-up, according to 17/20 participants. The average number of consultations were 6 in the first year, 4 in the second year and 3 in the third year of follow-up.

Follow-up diagnostics

In response to the question: "What kind of diagnostics are utilised during a routine follow-up consultation?", 17/20 participants answered that taking history and physical examination were standard. One participant also noted that radiologic imaging is standard for their follow-up consultations. Lastly, one participant noted that check-up appointments at the department of specialised dentistry are also part of their routine follow-up.

Discussion

In this survey study, the aim was to acquire an overview of the differences and similarities in midfacial defect management by different specialists in different dedicated oncological head and neck centres. To the best of our knowledge, this is the first survey on midfacial defect management after maxillectomy. Some participants would always treat midfacial defects with obturator prostheses (15%), but most participants would use both obturator prostheses and/or surgical reconstruction (70%).

Surgical reconstruction of midfacial defects can have high morbidity rates, donor site morbidity rates, prolonged surgical time and high costs [6]. Patients might prefer the less invasive obturator prosthetics for midfacial defect rehabilitation. Survey participants preferred conventional obturator prostheses (70%), implant-supported obturators prostheses (70%) and obturator prostheses with frame reconstruction (65%) almost equally. The drawbacks of conventional obturator prosthetics, like leakage, nasalance, difficulty swallowing, hygienic maintenance and frequent need of modification are well known, especially in large midfacial defects [6, 7]. If implant placement is possible, research suggests that the masticatory functionality and comfort in implant-supported obturator prosthetics are significantly better than conventional prosthetics. Implant-supported obturator prosthetics might even be a comparable alternative to surgical reconstruction [19], since implant-supported obturator prosthetics provide improved retention by additional anchorage [8, 20, 21].

Surgical reconstruction results in improved word intelligibility and masticatory efficiency over obturator prosthetics [22, 23]. Results on whether surgical reconstruction improves the quality of life over obturator prosthetics are contradictory though [24, 25].

Most survey participants preferred primary surgical reconstruction over secondary surgical reconstruction. Research suggests that secondary reconstruction is associated with higher rates of complication and lower rates of flap survival [26-28].

The survey participants employed a wide variety of different surgical reconstructive procedures for different Brown classes of midfacial defects. For Brown I defects, 'pedicled flaps' and 'radial forearm soft-tissue free-flaps' were preferred and for Brown II – VI defects, the 'fibular composite free-flap' and the 'iliac crest and internal oblique muscle free-flap' were preferred by most participants.

Currently, quantative meta-analyses on flap survival, quality of life and functionality outcomes between different surgical reconstructions of midfacial defects have not been published.

Advantages and disadvantages of different flaps are only descriptive [6]:
fibular composite free-flaps are reported to be versatile, reliable and aesthetically acceptable in cases that require bony restauration. However, they are reportedly less aesthetically desirable for reconstruction of orbital defects. The same is reported for radial composite forearm free-flaps. Scapular free-flaps are reported to be suitable for reconstruction of

palatal defects and orbital exenteration defects. Iliac composite free-flaps can provide a lot of bone if necessary, however differences in skin colour might be an aesthetic disadvantage.

Until clear recommendations from properly conducted randomized controlled trials can be made, a large variety of surgical reconstructive procedures will be used. The results of this study reflect that as well (Figure 2).

Preoperative 3D-planning helps reduce surgical reconstruction related problems, like higher morbidity rates, donor site morbidity rates, prolonged surgical time and high costs [6]. Ninety-three percent (13/14) of the survey participants utilised preoperative 3D-planning when this survey was conducted in late 2018. Developments in 3D-planning are moving quickly. Therefore, the survey participant who answered negatively to utilising 3D-planning was contacted again via e-mail in March 2021. The participant answered that from 2019 on, they started utilising 3D-planning in all their oncological reconstruction procedures, including midfacial defects. And thus, all centres who participated utilise 3D-planning for surgical reconstruction of the midface in the Netherlands now.

The average length of stay in different hospitals varied considerably (2 – 15 days). Although shorter hospital stays are less costly, it is unclear what length of hospital stay is ideal for the patient's recovery after maxillectomy (with/without primary surgical reconstruction). Notwithstanding that the length of stay might vary for individual patients with different tumour stages and surgical procedures.

Furthermore, follow-up consultation schedules were reportedly different between different hospitals (4 – 12 during the first year, 3 – 6 during the second year and 2 – 4 during the third year). This discrepancy might be explained by differences in counting consultations focused on (combinations of) wound healing, removing zygomatic wires, implant exposure procedures and prosthetic modifications. What all participants had in common, was that the frequency of follow-up consultations was reduced every subsequent year. Research suggests that there is no difference in overall survival between less intensive and more intensive follow-up, but more frequent visits might reduce time to detection of recurrence [29]. As of yet, no optimal follow-up consultation schedule has been determined.

Limitations

In total, 12 dedicated oncological head and neck cancer centres participated from Alkmaar, Amsterdam, Den Haag, Enschede, Groningen, Leiden, Maastricht, Nijmegen, Rotterdam and Utrecht. Our response rate was 77% (20/26), because two other cancer centres in the Netherlands did not respond to our survey invitations.

Two of the survey participants had not responded to two questions. While analysing these questions, these particular participants were deleted pairwise from the analysis.

Conclusion

This study provides an overview of midfacial defect management in the Netherlands. Most participants utilise both obturator prosthetics and surgical reconstruction for treatment of midfacial defects. A wide variety of reconstructive procedures are performed, but 'pedicled flaps' for Brown I and the 'fibular composite free-flap' for Brown II – VI were favoured most. Length of hospital stay and follow-up consultations also vary considerably across different hospitals.

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General summary and discussion

Introduction

Oral squamous cell carcinoma involving the maxilla (MSCC) is a rare subtype of oral cancer [1]. In oral cancer research, MSCC is often grouped with more prevalent subtypes of oral cancer, like squamous cell carcinoma of the tongue, floor of mouth or lower alveolar process [2-4]. Sample sizes for MSCC are usually very small which makes grouping understandable. However, grouping puts interpretation of study results at risk of bias via heterogeneity and confounding. After all, MSCC is quite distinct from other types of oral squamous cell carcinoma, because of the specific maxillary anatomy and the involvement of the midface in advanced stages.

Accordingly, this thesis set out to study multiple aspects of care for patients with MSCC to ultimately improve patient-specific care.

Key findings and implications

Detecting bone invasion

MSCC may invade adjacent bony structures and can even grow into the sinonasal cavities and beyond [5]. Surgical resection is the preferred treatment, so that complete removal of the tumour may be achieved [6, 7]. If bone invasion is present, en-bloc resection of the affected bone is necessary to achieve tumour free resection margins. Reliable imaging methods are essential for adequate planning of the surgical resection. Spiral Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have both been established as reliable imaging methods in oral cancer [8-11]. However, the reliability of spiral CT and MRI was primarily tested in either heterogeneous oral cancer groups in which MSCC patients were marginal subgroups [9, 11], or studies specifically focussed on mandibular invasion [8, 10].

That is why in chapter 1, the diagnostic value of spiral CT and MRI in detecting bone invasion of the maxilla was investigated. In the absence of metallic dental restorations, spiral CT could detect bone invasion more accurately than MRI; although this difference was not statistically significant. Therefore, during preoperative assessment the imaging method of choice may depend upon situational factors. Spiral CT might be preferable if the patient is less cooperative or claustrophobic. Limited clinical access to one imaging modality may also play a role; spiral CT-scans are generally cheaper and take less time to complete. On the other hand, MRI scans have low radiation burden and are less prone to imaging artefacts by metallic dental restorations and might therefore be preferable in certain cases [12-14].

An interesting development in CT-scanning is the Cone Beam Computed Tomography (CBCT). CBCT imaging requires less time, produces lower radiation dosage, generates higher spatial resolution and is available in most outpatient clinics. Furthermore, patients are not required to lay down, but can sit with their head in the natural position during the scanning procedure [15]. The value of CBCT in detecting bone invasion was previously tested in studies focussed on mandibular invasion [16, 17]. Hence, in chapter 2 the value of CBCT in detecting bone invasion of the maxilla was studied.

The results suggest that the accuracy of CBCT for the detection of bone invasion in MSCC patients was high, but observer dependent. There are two main causes of observer dependent differences. The first cause is differences in training and experience of the observers. Repeated training has been shown to improve the interpretation of imaging of several anomalies [18-20]. Joint evaluation of the scans and discussion might improve the diagnostic accuracy as well.

The second cause of observer dependent differences may be the (lack of) scoring criteria. Standardised scoring and reporting have been shown to improve the interpretation of scans of the appendix, pulmonary oedema and adnexal masses [21-23] and may help with the correct interpretation of imaging in general [24]. Our results suggest that the use of specific criteria improves the interpretation of CBCT imaging. As of yet, clear peer-reviewed guidelines are lacking for the interpretation and reporting of CBCT images of oral cancer. Formats for structured reporting of spiral CT and MRI images have been widely adopted by radiologists, to describe the location of the primary tumour and its volumetric dimensions, the extent of soft tissue involvement in all dimensions, the extent of bony involvement in all dimensions and the nodal status [23]. Similar formats for CBCT reports are not yet in place. A CBCT report format has been proposed for use by dentists in general practice [24]. This format mentions all anatomical subheadings that may be depicted on a CBCT scan: paranasal sinuses, nasal cavity, airway, cervical spine, temporomandibular joint, dental findings, other findings and recommendations.

Risk factors and treatment outcomes

In chapter 3, a systematic review and meta-analysis of different treatments, risk factors and outcomes of MSCC was discussed. The pooled 5-year local recurrence rate was comparable across the included studies.

The pooled 5-year overall survival rate was 53.7%. Some studies had noticeably lower survival rates, because their samples had a substantial proportion of cases with (chemo) radiotherapy as primary treatment [25-27] and a large proportion of cases with advanced tumour stages [26-29]. Furthermore, elective neck dissection was also associated with improved 5-year overall survival (OS) rates [30, 31].

In fact, the subgroup analysis of surgery only vs. surgery with (neo)adjuvant (chemo) radiotherapy resulted in a non-significant difference. This means that current (neo)adjuvant treatment protocols for adverse tumour characteristics successfully seem to improve overall survival rates for MSCC patients. Interestingly, the (neo)adjuvant treatment regimens were slightly different in all three studies of the subgroup analysis, but none were significantly better or worse [32-34].

One risk factor specific to MSCC was associated with lower rates of OS in multiple studies: posterior tumour extension defined as extension into the soft palate, infratemporal fossa, pterygoid muscles and pterygoid process [26, 33, 34].

Local recurrence and salvage treatment

Generally, locally recurrent tumours were the largest group of recurrent tumours in oral MSCC. Due to the complex anatomy, poor visibility and poor access, complete removal of maxillary tumours can be challenging, especially at the dorsal margins. In chapter 4, local recurrence and salvage treatment for MSCC were discussed in depth. Vascular invasion was significantly associated with the likelihood of local recurrence. There is currently no consensus on the optimal salvage treatment strategy for recurrent tumors involving the maxilla. Salvage surgery is often the treatment of choice, but it is frequently at the cost of morbidity and quality of life [35]. Furthermore, the type of salvage treatment was significantly associated with overall survival. Extensive salvage surgery should be considered with caution, as its value in survival may be debatable. Extensive salvage procedures may disturb the appearance and function while quality of life is particularly important in the final period of life.

Development and internal validation of a prediction model that can calculate overall mortality

Clinical parameters and the TNM-classification have been incorporated into prognostic models that calculate personalized survival probabilities of head and neck cancer patients in general, and for specific patient-groups, like octogenarian patients and advanced larynx cancer patients [36-39]. However, there were no prediction models that calculated the survival probabilities for MSCC patients specifically, nor were there prediction models that incorporated histopathological factors as predictors [36-41]. In chapter 5, statistically significant multivariate prediction models were successfully computed to calculate 2- and 5-year mortality probabilities with clinical- and histopathological predictors of MSCC-patients. The prediction models were statistically adjusted for the confounding effect of medical history and (lifestyle-related) comorbidities with the Charlson's comorbidity index [42]. Both adjusted prediction models had good to moderate results of predictive accuracy-tests and were recalibrated with the heuristic shrinkage factor [43-48]. The risk of distorted analysis results caused by the effects of selection bias and confounding were minimalised by analysing only the MSCC-subgroup and excluding other oral cavity cancer groups. The prediction models can be accessed easily via: mscc.oncologyheadneck.com

Figure 1: QR-code for quick access to the prediction models on mscc.oncologyheadneck.com.

Midfacial defect management – an e-survey on the clinical practice in the Netherlands

The extent of the resection determines the size of the subsequent midfacial defect. If the postoperative midfacial defect is not managed properly, the loss of orofacial function and cosmetic mutilation may lead to severe loss of health-related quality of life [49, 50]. The midfacial defect can be managed by the placement of an obturator prosthesis, or by surgical reconstruction with pedicled flaps or vascularized free-flaps.

There are currently no guidelines for evidence-based treatment options of midfacial defects. That is why a Dutch national e-survey was created. Twenty medical specialists in total (otolaryngologists and maxillofacial surgeons) participated and completed the survey. The questions contained in this survey covered various topics, such as: prosthetics, timing of surgical reconstruction, type of surgical reconstruction per class of midfacial defects.

Survey participants preferred conventional obturator prostheses, implant-supported obturators prostheses and obturator prostheses with frame reconstruction almost equally. If implant placement is possible, the masticatory functionality and comfort in implant-supported obturator prosthetics are significantly better than conventional prosthetics. Implant-supported obturator prostheses provide better anchorage and thereby improve retention [51-54]. However, results on whether (implant-supported) obturator prostheses improve the quality of life over surgical reconstruction are contradictory [55, 56]. Surgical reconstruction results in improved word intelligibility and masticatory efficiency over obturator prosthetics [57, 58].

Most survey participants preferred primary surgical reconstruction over secondary surgical reconstruction. Secondary reconstruction is associated with higher rates of complications and flap failure [59-61].

The survey participants employed a wide variety of different surgical reconstructive procedures for different Brown classes of midfacial defects. Our results demonstrated that 'pedicled flaps' for Brown I and the 'fibular composite free-flap' for Brown II – VI were favoured most.

Future perspectives

Detection of bone invasion

Various combinations of imaging modalities have previously been investigated and imaging-algorithms have been developed to detect bone invasion of the mandible [6]. Comparable studies for the detection of bone invasion of the maxilla have never been conducted. A study that compares different imaging algorithms might be an interesting subject for further study to improve the accurate detection of bone invasion of the maxilla.

Furthermore, the accuracy of CBCT for detecting bone invasion in MSCC and the interobserver agreement may improve by standardisation of interpretation and reporting of CBCT images. The incorporation of the essential CT/MRI reporting requirements of oral tumours [23] with the CBCT report format proposed by Miles et al. [24] might improve

the interpretation and interobserver agreement of CBCT images. This can be studied in a prospective trial with multiple observers scoring and reporting CBCT images for bone invasion in MSCC.

Prognostic prediction modelling in the future

Although the confounder-adjusted logistic models were successfully computed, internally validated and recalibrated, the performance generality should be tested and externally validated in another sample. This will constitute a challenge, because the incidence of MSCC is very low.

By using this developmental method of prediction model computation, more prediction models can be developed for other oral squamous cell carcinoma subtypes. Both patients and doctors would be greatly supported in their clinical decision-making if they have access to prediction models tailored to specific subtypes of oral squamous cell carcinoma.

These prediction models might be valuable tools in oral cancer care, if certain characteristics, like ease of use, accuracy and regular calibration are prioritised and safeguarded.

General limitations

Researching MSCC is generally limited by the low incidence of MSCC [1]. This generally means two things: most studies have small sample sizes and most studies are retrospective in nature.

In this thesis, the largest sample of analysed patients consisted of only 95 cases (chapter 4, 5). Although this number may seem big to some, in actuality a sample of 95 cases is small. These 95 cases were patients that were operated in a time span of 15 years (between 2000 – 2015). In other words, on average 6.3 MSCC patients were eligible for inclusion per year in the University Medical Center of Utrecht. Unfortunately, 6.3 patients per year does not constitute enough patient volume in order to perform prospective studies. Retrospective studies are at risk of information bias and therefore lower in rank of evidence.

As a result, multicentre prospective studies are needed. In the Netherlands almost all head and neck cancer patients are treated in the 8 major head and neck centers and 6 preferred partners of the Dutch Head and Neck Society (NWHHT). Within the NWHHT many multicentre studies were conducted, allowing for successful prospective studies also in rare head and neck cancer subtypes, e.g., MSCC.

Establishing specialised maxillary cancer care centers with a dedicated maxillary cancer team might improve patient volume and quality of care. After all, high patient volumes in specialized cancer centres are associated with better survival outcomes [62-64].

Accordingly, higher patient volumes might have beneficial effects on treatment outcomes and would facilitate research to be conducted for MSCC patients as well [65, 66].

General conclusions

In this thesis, several aspects of clinical care for MSCC patients were studied. The aim was to ultimately improve MSCC patient-specific care. The main findings are as follows:

- Both CT and CBCT are very accurate imaging methods to detect maxillary bone invasion. However, MRI is a suitable alternative if contraindications for CT are present or MRI is already made for other indications.
- The best treatment of MSCC available today is probably surgery including elective neck dissection, and adjuvant (chemo)radiation in case adverse tumour characteristics are present.
- Salvage surgery prolongs overall survival in case of small recurrence, but might have dubious value in survival regarding larger recurrences infiltrating adjacent facial structures.
- The overall 2- and 5-year mortality probability of MSCC can now be calculated with newly computed prediction models.
- A wide variety of reconstructive procedures are performed, but 'pedicled flaps' for Brown I and the 'fibular composite free-flap' for Brown II – VI were favoured most among Dutch specialists.

Nederlandse Samenvatting en Discussie

Introductie

Het plaveiselcelcarcinoom van de bovenkaak (de Engelse afkorting is MSCC) is een zeldzaam type mondholtekanker [1]. Omdat MSCC zo zeldzaam is, worden patiënten met MSCC in onderzoek vaak gecombineerd met patiënten die mondholtekanker hebben op andere plekken in de mond, zoals de tong, of de mondbodem [2-4]. Omdat er weinig patiënten zijn met MSCC is dit ook begrijpelijk. Hierdoor kan echter bias ontstaan, waardoor de resultaten van onderzoek over MSCC verkeerd geïnterpreteerd kunnen worden. In deze dissertatie werden meerdere aspecten van het behandeltraject van patiënten met MSCC onderzocht, met als doel om hiermee de zorg voor deze patiënten te verbeteren.

Belangrijkste bevindingen en implicaties

Botinvasie vaststellen

MSCC groeit vaak in naastliggend bot, in de sinonasale holtes van het aangezicht, of zelfs daar doorheen [5]. Chirurgische resectie van MSCC is de eerste keuze van een in opzet curatieve behandeling. Het doel van deze behandeling is om de tumor volledig te verwijderen [6, 7]. Als de tumor in naastliggend bot gegroeid is, zal ook een deel van het bot verwijderd moeten worden. Het is daarom belangrijk vast te stellen of er sprake is van ingroei in het bot [8-11].

In hoofdstuk 1 van deze dissertatie werd onderzocht of met spiraal-CT en MRI kan worden vastgesteld of botinvasie van de bovenkaak aanwezig was. In eerdere onderzoeken was het herkennen van botinvasie met spiraal-CT en MRI onderzocht in heterogene patiëntengroepen [9, 11], of onderzocht op patiënten met kanker van de onderkaak [8, 10]. In hoofdstuk 1 werd aangetoond dat zowel met spiraal-CT, als met MRI, botinvasie van de bovenkaak herkend kon worden. Daarom zal de keuze voor de beeldvorming afhankelijk zijn van situationele factoren. Zo is spiraal-CT meer geschikt voor minder coöperatieve patiënten of voor patiënten met claustrofobie, omdat scans gemakkelijker en sneller gemaakt kunnen worden. Tevens is spiraal-CT goedkoper dan MRI. Het voordeel van MRI is dat het een lagere stralingsbelasting heeft en dat er minder vaak beeldartefacten ten gevolge van dentale restauraties ontstaan, die de interpretatie bemoeilijken [12-14]. Daarnaast geeft MRI meer informatie over uitbreiding van de tumor in de weke delen.

Een interessante ontwikkeling in CT-beeldvorming is de Cone Beam CT (CBCT). Het voordeel van CBCT-beeldvorming is dat het vervaardigen van een scan minder tijd kost dan het vervaardigen van een spiraal-CT. Ook heeft CBCT een lagere stralingsbelasting, een hogere resolutie en is bovendien beschikbaar in de meeste kaakchirurgische poliklinieken. Bovendien kan de scan zittend worden gemaakt met het hoofd van de patiënt in een natuurlijke rustpositie [15]. In hoofdstuk 2 van deze dissertatie werd onderzocht of botinvasie van de bovenkaak gedetecteerd kon worden met CBCT [16, 17].

De resultaten van hoofdstuk 2 laten zien dat met een CBCT zeer nauwkeurig botinvasie vastgesteld kan worden. De resultaten waren echter observant-afhankelijk. Er zijn twee

oorzaken waarom resultaten observant-afhankelijk kunnen zijn. De eerste reden is training en ervaring. Hoe meer training en ervaring een observant heeft, hoe beter de interpretatie zal zijn [18-20]. De tweede reden is dat er voor CBCT momenteel nog geen gestandaardiseerde wijze van beoordelen bestaat. Uit onderzoek blijkt dat gestandaardiseerde scoreformulieren helpen met correcte interpretatie van medische beeldvorming. Specifieke criteria dragen bij aan de nauwkeurigheid van de interpretatie en verslaglegging [21-23]. Momenteel zijn er geen wetenschappelijke richtlijnen voor de interpretatie van CBCT-scans. Een suggestie voor een standaard CBCT-verslag is wel gepubliceerd [24], maar nooit gevalideerd. Dit format is gemakkelijk te combineren met de minimaal vereiste beschrijving van de tumor voor CT- en MRI-verslagen [23] en is derhalve een interessant onderwerp voor toekomstig onderzoek.

Risicofactoren en behandeluitkomsten

Hoofdstuk 3 beschrijft een systematische review en meta-analyse over MSCC. De meeste artikelen hadden vergelijkbare cijfers van lokale tumor recidieven. Uit de meta-analyse bleek dat de samengenomen vijfjaarsoverleving 53.7% was. Sommige studies hadden echter duidelijk lagere overlevingscijfers. Dit kan worden verklaard door een groot percentage aan patiënten die ofwel niet chirurgisch behandeld zijn aan hun tumor [25-27], ofwel omdat zij een tumor hadden in een vergevorderd stadium [26-29].

Tevens toonden meerdere studies een associatie van lymfekliermetastasen in de hals met lagere overlevingscijfers. Bij afwezigheid van lymfekliermetastasen in de hals (cN0) tijdens de preoperatieve stadiëring werd electieve halsklierdissectie geassocieerd met een betere kans op overleving [30, 31].

Bovendien bleek uit een subgroep analyse dat patiënten die behandeld werden met chirurgische resectie en (neo)adjuvante therapie vanwege ongunstige tumor eigenschappen, een statistisch vergelijkbare overlevingskans hebben als patiënten die alleen chirurgisch behandeld zijn. Er lijkt vooralsnog geen verschil te zijn in effectiviteit tussen verschillende varianten van (neo)adjuvante therapie [32-34].

Thans is er door meerdere studies een MSCC-specifieke risicofactor geïdentificeerd die een negatieve invloed lijkt te hebben op de overleving: posterieure tumor uitbreiding, gedefinieerd als groei in het palatum molle, fossa infratemporale, musculi pterygoidei en de processus pterygoideus [26, 33, 34].

Lokaal recidief en salvage-chirurgie

De meeste recidieven na maxillectomie bleken lokaal voor te komen, dat wil zeggen in het gebied van de primaire resectie. Complete verwijdering van een MSCC-tumor wordt bemoeilijkt door de complexe anatomie, beperkte visualisatie en beperkte toegankelijkheid. In hoofdstuk 4 werden lokale recidieven en salvage-chirurgie besproken. In onze studie was vaso-invasie bij MSCC significant geassocieerd met een verhoogde kans op lokaal recidief. Chirurgie wordt beschouwd als beste behandeloptie voor een recidief [35]. Chirurgie van recidief tumor gaat echter vaak ten koste van de kwaliteit van leven, doordat de chirurgische

resectie meestal groot is. 'Salvage' chirurgie bij een recidief tumor verlengt algehele overleving alleen bij kleine tumoren; het resultaat bij grote recidieftumoren is dubieus. Uitgebreide salvage chirurgie zou daarom met enige terughoudendheid geadviseerd moeten worden. Verlies van kwaliteit van leven in de laatste fase van het leven is een belangrijke factor bij de overweging om al dan niet salvage chirurgie te verrichten.

De ontwikkeling en interne validatie van een predictiemodel dat overleving kan voorspellen

Klinische parameters en de TNM-classificatie zijn eerder gebruikt voor de ontwikkeling van predictiemodellen die overleving voorspellen van patiënten met hoofdhalskanker [36-39]. Er zijn echter geen predictiemodellen ontwikkeld voor de overlevingskansen van patiënten met MSCC. Noch zijn er studies die histopathologische factoren incorporeren in hun modellen [36-41]. Daarom zijn in hoofdstuk 5 statistisch significante predictiemodellen gecomputeerd, zodat de 2- en 5-jarige overlevingskansen van patiënten met MSCC voorspeld kunnen worden met klinische en histopathologische variabelen. De modellen zijn gecorrigeerd voor medische voorgeschiedenis en comorbiditeit middels de inclusie van de Charlson's comorbidity index in het model [42]. De ontwikkelde predictiemodellen scoren gemiddeld tot goede testresultaten op nauwkeurigheid en zijn gerecalibreerd met de 'heuristic shrinkage factor' [43-48]. Deze predictiemodellen zijn ontwikkeld op basis van data van louter patiënten met MSCC. Het risico op foutieve resultaten op basis van selectiebias is dan ook op zeer laag ingeschat. De predictiemodellen zijn te gebruiken via de website: mscc.oncologyheadneck.com.

Figure 1: QR-code waarmee de predictiemodellen gemakkelijk bezocht kunnen worden op mscc.oncologyheadneck.com.

Midfaciaal defect management – Nederlandse enquête

De chirurgische resectie bepaalt de grootte van het defect in het middengezicht. Wanneer het defect in het middengezicht niet goed behandeld wordt zal het verlies van orofaciale functie en cosmetiek leiden tot ernstig verlies in kwaliteit van leven [49, 50]. Management van het defect in het middengezicht kan met zowel een obturator-prothese als chirurgische reconstructie middels gesteelde lappen of vrij-gevascularisseerde lappen.

Er zijn momenteel geen richtlijnen waarin 'evidence-based' behandeladviezen worden gegeven over de behandeling van defecten in het middengezicht. Daarvoor werd een enquête gemaakt, waaraan 20 Nederlandse medisch specialisten (KNO-artsen en MKA-chirurgen) hebben meegedaan. In deze enquête werden onder andere vragen gesteld over de volgende onderwerpen: type protheses, timing van chirurgische reconstructies en type chirurgische reconstructie per klasse defect in het middengezicht.

De surveyanten hadden geen voorkeur voor conventionele protheses of implantaat-gedragen protheses of frame-gedragen protheses. Implantaat-gedragen protheses hebben significant betere verankering en retentie van de prothese [51-54]. Het is vooralsnog onduidelijk of een implantaat-gedragen prothese daadwerkelijk de kwaliteit van leven voor patiënten verbetert ten opzichte van patiënten met een chirurgische reconstructie [55, 56]. Chirurgische reconstructie lijkt daarentegen het herstel van de verstaanbaarheid en het kauwvermogen te bespoedigen ten opzichte van obturator-protheses [57, 58].

Het merendeel van de surveyanten hadden de voorkeur voor primaire reconstructie ten opzichte van een secundaire reconstructie. Uit onderzoek blijkt dat secundaire reconstructies een hoger risico hebben op complicaties en verlies van reconstructieve lappen [59, 60, 61].

De surveyanten gebruikten veel verschillende reconstructieve methodes voor patiënten met MSCC. Voor patiënten met een Brown I defect werden met name gesteelde lappen toegepast. Voor patiënten met Brown II – VI werden met name vrij-gevascularisseerde samengestelde fibula-lappen gebruikt.

Met het oog op de toekomst

Herkennen van botinvasie

Voor de detectie van botinvasie van de onderkaak zijn diverse combinaties van beeldvormend onderzoek onderzocht en zijn algoritmes ontwikkeld. [6]. Een dergelijk onderzoek voor invasie van de bovenkaak is nooit uitgevoerd. Een studie die verschillende diagnostische algoritmes met elkaar vergelijkt is een interessant aanknopingspunt voor verder onderzoek om de detectie van botinvasie van de bovenkaak te verbeteren.

In deze dissertatie is ook vastgesteld dat CBCT zeer nauwkeurig is, echter bleek er verschil in nauwkeurigheid te zijn tussen de verschillende beoordelaars. Daarom is een vergelijkende studie naar het effect van gestandaardiseerde scoring en verslagslegging op de nauwkeurigheid van de beoordeling van CBCT een interessant onderwerp voor verder

onderzoek. Hiervoor zouden het concept CBCT-verslag van Miles et al. [24] en de basale vereisten voor verslaglegging van orale tumoren [23] als basis kunnen dienen.

Prognose berekenen in de toekomst

Hoewel de ontwikkeling van de predictiemodellen in deze dissertatie succesvol zijn verlopen, is het noodzakelijk dat de predictiemodellen worden getoetst aan de hand van een externe dataset. Dit zal echter een uitdaging zijn, gezien de lage incidentie van MSCC.

Daarentegen kan de gebruikte methode van modelontwikkeling ook toegepast worden bij andere patiëntgroepen met mondholtekanker. Zowel de patiënt als de arts zouden gebaat zijn bij het bestaan van dergelijke specifieke modellen; ieder model toegespitst op een subtype van mondholtekanker.

Dergelijke predictiemodellen zouden kunnen dienen als handige hulpmiddelen bij de behandeling van mondholtekanker, mits er bij de ontwikkeling voldoende aandacht is voor eigenschappen als gebruikersgemak, nauwkeurigheid en kalibratie.

Algemene limitaties

Onderzoek naar MSCC is uitdagend, omdat de incidentie van MSCC erg laag is [1]. In algemene zin heeft dit twee consequenties: de meeste studies hebben een kleine groepsgrootte en de meeste studies zijn retrospectief van aard.

De grootste groep uit deze dissertatie bestaat uit 95 geanalyseerde patiënten (hoofdstuk 4, 5). Hoewel een aantal van 95 patiënten met tumor van de bovenkaak relatief veel is vergeleken met andere onderzoeken, is 95 voor statistische analyse een klein aantal. Tumoren van de bovenkaak komen niet veel voor, hetgeen ook blijkt uit het feit dat deze 95 patiënten verzameld zijn van operatielijsten van de afgelopen 15 jaar (2000-2015). Anders gezegd, gemiddeld worden 6,3 patiënten met MSCC per jaar behandeld in het UMC Utrecht. Het meeste onderzoek was ook nog eens retrospectief onderzoek, hetgeen onderhevig is aan informatiebias met lagere bewijslast. Voor onderzoek met hogere bewijslast is een prospectieve opzet nodig met meer patiënten, waarvoor samenwerking met andere hoofd-hals centra vereist is. In Nederland is de zorg voor hoofdhalskankerpatiënten gecentraliseerd binnen de 8 hoofdcentra en 6 zogenaamde 'preferred partner' centra van de Nederlandse Werkgroep Hoofd-Hals Tumoren (NWHHT), waarbinnen veel multicenter-onderzoek plaatsvindt. Bepaalde centra zouden kunnen worden aangewezen als expertisecentra met toegewijde behandelteams voor patiënten met maxilla-tumoren. Het is immers vastgesteld dat de zorgkwaliteit in gespecialiseerde centra verbetert en leidt tot hogere overlevingscijfers [62-64]. Zo kan niet alleen de zorgkwaliteit verbeterd worden, maar vergemakkelijkt dit ook het verrichten van prospectief multicenter-onderzoek [65, 66].

Algemene conclusies

Verscheidene aspecten van klinische zorg voor patiënten met MSCC zijn aan bod gekomen in deze dissertatie. Het doel van deze dissertatie was verbetering van de zorg voor patiënten met MSCC:

- Zowel CT als CBCT bleken zeer nauwkeurige beeldvormende technieken te zijn om botinvasie van de maxilla mee vast te stellen. MRI blijft echter een geschikt alternatief indien contra-indicaties voor CT aanwezig zijn of reeds een MRI vervaardigd is voor andere indicaties.
- De beste behandeling voor MSCC is momenteel chirurgische resectie van primaire tumor gecombineerd met halsklierdissectie en adjuvant (chemo)radiatie.
- 'Salvage' chirurgie bij een recidief tumor verlengt algehele overleving alleen bij kleine tumoren; het resultaat bij grote recidieftumoren is dubieus.
- Predictiemodellen waarmee de 2- en 5-jaars overlevingskans voorspeld kunnen worden zijn met succes ontwikkeld en intern gevalideerd.
- Er worden veel verschillende manieren van midfaciale reconstructie gebruikt, maar gesteelde lappen voor Brown I en vrije samengestelde fibulalappen voor Brown II-VI worden het meest toegepast.

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Appendices

Curriculum Vitae Auctoris

Fons Joeri Bernard Slieker is op 5 mei 1992 geboren op de Baarsjesweg in Amsterdam. Fons was getogen te Hilversum, waar hij in 2010 afstudeerde aan het Gymnasium van het Alberdingk Thijm College. Hij begon daarna met zijn opleiding Geneeskunde aan de Universiteit Utrecht. Tijdens zijn opleiding ondernam Fons meerdere extra-curriculaire activiteiten, zoals een cursus Wetenschapsfilosofie van Studium Generale. Ook was hij betrokken bij de studievereniging MSFU "Sams", de Utrechtse Studenten Roeivereniging "Triton", het onafhankelijk medisch herendispuut "DAS" en de boeddhistisch-humanistische organisatie Soka Gakkai Nederland. Enkele hoogtepunten waren de organisatie van de Hollandia Roeiwedstrijden NK Klein in 2015 en de organisatie van de Nationale Studenten Roeiwedstrijden 'Varsity' 134 in 2017.

Gedurende zijn opleiding geneeskunde werd zijn interesse gewekt in de heelkunde en in het bijzonder de mond- kaak- en aangezichtschirurgie. Fons raakte betrokken bij meerdere onderzoeksprojecten bij de algemene heelkunde en de chirurgische hoofd-hals oncologie. Na het voltooien van zijn opleiding in 2018, zette hij zijn onderzoeksactiviteiten voort als arts-onderzoeker bij de vaatchirurgie. Hier coördineerde Fons gedurende één jaar een experimenteel traject, waarbij het behandelen van arteriële plaques met gefocust echogeluid werd onderzocht.

Na één jaar werkzaam te zijn geweest als arts-onderzoeker, werd Fons toegelaten tot de specialistenopleiding van de mond- kaak- en aangezichtschirurgie. Hij startte in 2019 de vooropleiding 'tandheelkunde voor artsen' aan de Radboud Universiteit te Nijmegen. Daarnaast was hij tijdens zijn vooropleiding werkzaam als vaccinatie-arts en injectables-arts. Onder begeleiding van prof. dr. de Bree en dr. Van Cann, bleef Fons werken aan zijn onderzoek naar het carcinoom van de maxilla, wat uiteindelijk resulteerde in het huidig proefschrift.

Op 1 maart 2022 zal Fons zijn specialistenopleiding tot mond- kaak en aangezichtschirurg voortzetten.

Publications

van Ginkel JH, Slieker FJB, de Bree R, van Es RJJ, Van Cann EM, Willems SM. (2017). Cell-free nucleic acids in body fluids as biomarkers for the prediction and early detection of recurrent head and neck cancer: A systematic review of the literature. Oral Oncol. 75: 8-15.

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[EINDE BERICHT]