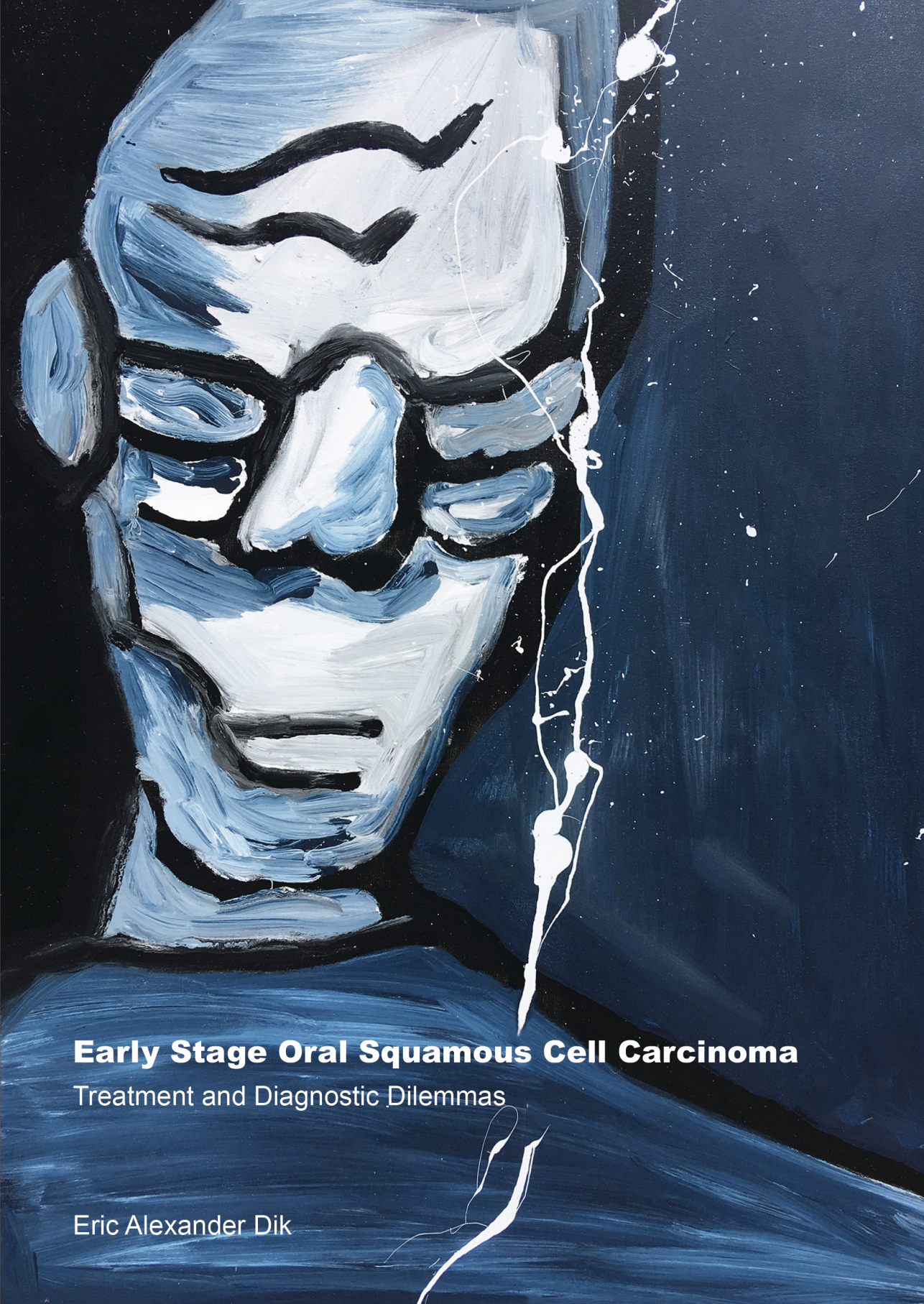

Early Stage Oral Squamous Cell Carcinoma

Treatment and Diagnostic Dilemmas

Eric Alexander Dik

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Treatment and Diagnostic Dilemmas

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CHAPTER ONE

General introduction and outline

Introduction

In the Netherlands, head and neck cancer is the 7th respectively 9th most common malignancy in men (3.6%) and women (2.0%)[1]. Thirty percent of the head and neck tumors are oral squamous cell carcinoma (OSCC)[1]. The incidence of OSCC in the Netherlands almost doubled the last 25 years from 506 new patients per year in 1990 to 940 in 2017[1]. Senescence of the Dutch population partially explains this increase of OSCC patients[1]. At the same time, survival rates hardly improved, with a five-year overall survival rate of 56% in 1989 and 61% in 2012[1]. Elderly patients have an increased risk of morbidity and mortality[2], which might explain these disappointing survival rates. However, the observed survival is corrected for the expected mortality based on the Dutch population, based on gender and calendar year[3]. So, despite all our scientific efforts and promising novel diagnostic and therapeutic techniques[4-6], there has not been a substantial improvement in survival over the last three decades. To optimize future treatment results, it is relevant to critically review current diagnostic techniques and treatment strategies. To gain insight into the results of these strategies with respect to loco-regional recurrence and survival.

Staging of oral squamous cell carcinoma

Patients presenting with an OSCC are staged to establish the local extension of the tumor and to investigate regional and distant metastasis. A biopsy is performed to confirm the diagnosis OSCC. Subsequently, staging in most head and neck oncology centers in the Netherlands consists of a combination of physical examination and imaging by Magnetic Resonance Imaging (MRI) and/or Computer Tomography (CT) of the head and neck area, Ultrasound (US) of neck nodes, accompanied by a fine needle aspiration cytology (FNAC) of suspect lymph-nodes on indication and a routine chest X-ray with a thoracic CT scan on indication. Treatment planning is classically based on this primary staging. Additionally, a sentinel node biopsy procedure is applied in an increasing number of head and neck centers over the world as a diagnostic tool to identify occult neck nodal metastasis[7, 8].

Current treatment strategies of early stage oral squamous cell carcinoma

Local approach

This thesis focuses on early stage oral OSCC's i.e. cT1-2 tumors with a clinically negative (cN0) neck. There is consensus on the initial local approach of a patient with an early stage OSCC. The first choice of treatment is complete surgical removal with a sufficient resection margin (i.e. traditionally ≥5mm clear margins)[9, 10]. In clinical practice, resection margins are not always sufficient. Fifteen to 63% of the tumors are resected with close margins[11-13]. The presence of tumor cells close (>0-5 mm) to the resection margin after the primary resection and the necessity and type of additional treatment is a matter of repeated debate[14, 15]. The risk of local recurrence in case of close margins must be weighed against the effectiveness and potential side effects of local adjuvant treatment. Instead of watchful follow-up, adjuvant treatment can

consist either of an additional resection of the area with a close margin or post-operative radiotherapy (PORT).

Regional approach

Besides concerns for local tumor treatment, the regional approach is even more important because of its prognostic implications[16]. Even small OSCC's may behave aggressively by metastasizing regionally and eventually to distant sites[17, 18]. Currently, clinicians are not able to detect all cervical metastasis by primary staging. In case of a cN0 neck, about 20-40% of the necks still contain occult nodal metastasis[5, 19, 20]. Because the presence of (occult) nodal metastasis is pivotal to prognosis, there is consensus that the neck should be treated prophylactically or monitored closely. In practice three approaches are possible: watchful waiting, a sentinel node procedure or a selective neck dissection levels I-III[21, 22]. Novel promising techniques such as gene expression- or protein-profiling of the primary tumor are still not applicable in routine clinical practice. However, they may be of added value in the prediction of neck nodal metastasis in the future[6, 23].

Outline of this thesis

The goal of OSCC treatment is to pair maximal loco-regional tumor control with a minimum of iatrogenic side effects, while considering the patient's co-morbidity, age and wishes. In literature, there is much evidence for several loco-regional treatment options for OSCC's, such as wide excision of the primary tumor for maximal local tumor control[24, 25], and the (selective) neck dissection to gain the best regional tumor control[21, 26]. This knowledge improved the survival of OSCC patients[26]. On the other hand, there is a delicate balance between over- and under-treatment[27]. For instance, 60-80% of the T1-2 OSCC's in the Netherlands have no regional metastasis, hence a neck dissection is not always necessary[19, 20]. To identify those patients who need a more extensive treatment and those who do not, remains a challenge. To reduce unnecessary side effects to a minimum, cancer care should be as personalized as possible. However, how to create such care is not always clear and provides ongoing discussions in literature. Topics such as the importance of tumor differentiation grade, the relevance of margin status >5mm, and the potential need for a selective neck dissection in case of a clinically negative neck, all play a role in daily clinical practice and are subject of discussion considering the choice of the optimal treatment modality for the individual patient. Unfortunately, evidence is inconclusive and often contradictory[28-31].

Main focus of this thesis

This thesis addresses some key topics that play a central role in frequent discussions within multidisciplinary head and neck cancer boards, such as the diagnostic value of the biopsy, the prognostic value of specific unfavorable histological growth parameters, the consequences of close resection margins and the best approach for

the clinically negative neck. The goal of this thesis is to find evidence, for frequently used treatment modalities, uncover shortcomings to refine current treatment options, to support daily decision making during the treatment of early stage OSCC.

The role of the biopsy

Before treatment of an early stage OSCC, a biopsy is performed to confirm the clinical diagnosis. After the tumor resection a selection of predefined histological variables are reported by the head and neck pathologist[3]. Indeed, a selection of specific growth parameters, i.e. infiltrative growth (IG), vascular invasive growth (VG) and perineural growth (PG) are significantly related to the occurrence of neck nodal metastasis and outcome[14,19]. The relation between these growth parameters and nodal status however, is mainly based on the growth parameters derived from the definite resection specimen. Reliable knowledge of these parameters before treatment, on the biopsy specimen, could be helpful in deciding the optimal loco-regional therapy. This could lead to a more patient specific treatment planning, reduce over- or under treatment and perhaps may yield better outcome. Determination of growth parameters on the biopsy specimen is not a daily routine in many head and neck centers. Before using the growth parameters of a biopsy to guide further treatment planning, it is important to know its reliability in terms of its representativeness in the definite resection specimen. **In Chapter 2** the histological growth parameters determined on the biopsy and the resection specimen will be related to N-status and survival, to gain insight in the value of the biopsy in relation to treatment planning of the neck. The aims of this retrospective study are to evaluate whether the presence or absence of the histologic parameters IG, VG and PG in the preoperative biopsy correlate with the resection specimen and to compare the presence of these parameters between lymph node–positive and lymph node–negative patients. In contrast to the determination of growth parameters, the biopsy and resection specimen are routinely graded in many head and neck clinics. The Broders grading system is easy to use, well known and popular among pathologists[32, 33]. It utilizes four differentiation grades: Well, Moderately, Poorly and Undifferentiated. According to several authors, deterioration of grade is related to more aggressive tumor behavior and worse outcome[29, 32]. However this relation is controversial[30, 34]. **Chapter 3** focuses on the determination of differentiation grade on the biopsy and resection specimen. This study will determine the correlation between differentiation grade of the biopsy and resection specimen in stage I and II OSCC's. Furthermore, it correlates differentiation grade of the resection specimen with other growth parameters, nodal stage and survival.

The role of the pathologist, inter-observer variability

Pathological tumor characteristics, such as margin status, bony involvement (BI) and the presence of "unfavorable" growth parameters i.e. infiltrative growth (IG), perineural growth (PG) and vascular invasive growth (VG), are worldwide important prognostic factors for the risk on recurrent disease[11,35-37]. The decision whether to perform an adjuvant treatment i.e. postoperative radiotherapy (PORT) or re-resection, is mainly based on these parameters[3]. This makes the pathology report a leading diagnostic tool in deciding whether to perform adjuvant treatment after primary surgery. Since adjuvant treatment modalities are accompanied by serious side effects[38, 39], it is of importance that clinicians can rely on the quality of the pathological report of the resection specimen, regarding both the primary tumor and the nodal metastasis. Pathological observations should be reproducible from one pathologist to another to have substantial validity[40]. The pathological scoring of growth parameters in the tumor tissue is increasingly done on digital slides. To estimate the reproducibility and subsequently the reliability of histological parameters, knowledge of the inter observer variability (IOV) of these parameters scored on digital slides is relevant. A high IOV is a well-known phenomenon in the determination of differentiation grade (i.e. well, moderate, poor, undifferentiated) of OSCC's[32, 40, 41]. However, in literature, information about the IOV for the parameters BI, IG, PG and VG is more scarce**. Chapter 4 describes** a multicenter study with six pathologists of six Dutch head and neck centers re-assessing digitalized histological sections of OSCC's. The aim of this study is to assess the IOV within this group of expert head and neck pathologists in the Netherlands in order to estimate reproducibility and reliability of the pathological report.

Treatment of the primary tumor

If tumor cells are present in the resection margin, adjuvant treatment is generally advised[10, 13, 42]. However, if resection margins are clear but tumor cells are close to the border, discussion arises about the necessity of adjuvant treatment. The presence of "unfavorable" pathological growth parameters (i.e. IG, VG and PG) in combination with close margins (>0-5mm) increases doubt about the presence of residual disease. Different local adjuvant treatment modalities are available with their specific side effects[11]. In the Netherlands, these decisions are still based on a more than 20-year-old algorithm of "intermediate risk criteria"[3, 43]. Intermediate risk criteria for OSCC's are close margins, IG, VG, PG and BI[3]. The presence of ≥3 intermediate risk criteria would increase the risk of local recurrence, which is an indication for PORT or re-resection[12, 44,43]. Up to now, randomized controlled trials that support this local recurrence concept are lacking**.** The results of local adjuvant treatment after primary resection with close margins will therefore be evaluated in **Chapter 5**. Local recurrences are related to margin status, histological parameters and adjuvant treatment modality. Three modalities for local adjuvant approach in case of close margins (>0-5mm) will be evaluated: watchful waiting, re-resection or PORT. These results will be compared with those of resected early stage OSCC with margins >5mm, designated as "free" margins. The evidence for one modality above another in relation to pathological growth parameters is subsequently determined.

Treatment of the neck

There is still an ongoing debate about the approach of the cN0 neck. A clinically negative neck is no guarantee for a true negative neck: around 20-40% of the clinically negative necks still contain metastasis[19, 26, 45, 46]. Still, we do not fully understand the biological behavior of OSCC's. Some tumors disseminate at an early stage, while others grow extensively locally and do not metastasize. Several clinical/pathological features seem related to the ability to recur loco-regionally[14, 15, 19, 30]. As stated earlier, novel diagnostic entities like genetic- and protein-profiling are promising, but not yet reliable enough for routine use in daily practice[5]. Until now, the decision whether to treat the clinically negative neck is mainly based on the diameter of the primary tumor and its estimated depth of invasion during physical examination and imaging[3]. In general, three different approaches for the clinically negative neck in oral cancer are possible: sentinel node biopsy (SNB), selective neck dissection levels I, II and III (SND) or watchful waiting of the neck (WW). In case of positive node(s) definite treatment (i.e. SND) is still mandatory[45]. Since we are not able yet to distinguish regionally aggressive OSCC's from those who do not metastasize, there is a constant tension between over- and undertreatment. This leads to either unnecessary invasive treatment of the neck if nodal metastasis are absent or, when a watchful waiting policy was adopted, overt metastasis during follow up with a worse prognosis and treatment with more morbidity[21]. **Chapter 6** will focus on the clinically negative neck. The aim of this retrospective study is to evaluate a treatment strategy for the cN0 neck in stage I-II OSCC at the department of Oral and Maxillofacial surgery of the University Medical Centre Utrecht. This strategy consists of a selective neck dissection for cT1–T2N0M0 OSCCs and watchful waiting in case of cT1N0M0 OSCCs with a diameter of <15mm and an estimated invasion depth of <5mm. The distribution of occult metastases, the incidence of extra capsular spread (ECS), and survival rates will be analyzed.

Prognosis after primary surgical therapy and adjuvant treatment. A Nomogram

In most cases, primary treatment of an OSCC consists of loco-regional surgery. In a substantial number of cases there is an indication for adjuvant therapy[11]. These adjuvant therapies have additional morbidity and side effects[38, 39, 47]. Moreover, because of senescence, the population with a newly diagnosed OSCC is getting older[1]. Extensive adjuvant therapy is not always desirable because of substantial co-morbidity or the patients' wishes. Insight in prognosis after primary surgical treatment is therefore important. Until now, the prognosis is mainly based on the TNM staging system[48]. The system has been successfully used for staging and treatment planning. Unfortunately, the TNM-7 system did not incorporate specific patient and personalized tumor characteristics. As a result, a more individually based treatment planning seems warranted. A proposal for a new prognostic model is presented in **Chapter 7.**

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2

CHAPTER TWO

Poor correlation of histologic parameters between biopsy and resection specimen in early stage oral squamous cell carcinoma

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ABSTRACT

Objectives Infiltration depth, perineural growth (PG), vascular invasive growth (VG), and infiltrative growth (IG) are associated with regional metastases in oral squamous cell carcinomas (OSCCs). Preoperative knowledge of these parameters could facilitate the treatment planning of the neck. The aim of this study was to evaluate if the biopsy specimen correlates with the resection specimen.

Methods In total, 149 patients with a pT1-2cN0 OSCC were included. Biopsy thickness and tumor thickness were analyzed. Occurrence of PG, VG, and IG was determined on biopsy and resection specimens and correlated with the N status and survival. Sensitivity, specificity, positive and negative predictive value, and diagnostic gain of the biopsy specimen were calculated.

Results N+ patients showed PG, VG, and IG significantly more often in the resection specimen compared with N– patients (P = .02, P = .001, and P = .001, respectively). Histologic parameters in the biopsy specimens did not correlate with N status or survival. The positive diagnostic gain for biopsy specimens with PG, VG, and IG was 57%, 40%, and 19%, respectively. The negative diagnostic gain was 2%, 0%, and 22%, respectively.

Conclusions Histologic parameters in biopsy specimens do not represent the resection specimen. Determination of histologic parameters in routinely taken biopsy specimens of OSCC is not helpful in deciding whether to treat the neck.

Introduction

Management of the clinically negative neck (cN0) in early stage oral squamous cell carcinomas (OSCCs) is still an issue of debate[1-5]. It is estimated that around 20% to 40% of the cN0 necks of early stage OSCC contain occult metastases[3,5-7]. In today's clinical practice, the neck is staged by a combination of physical examination (palpation) and imaging (computed tomography, magnetic resonance imaging, ultrasonography). The accuracy of these examination techniques to detect small metastases varies from 40% to 80%[4,7-9]. Consequently, some patients are exposed to an unnecessary selective neck dissection, while others are left untreated and confronted with overt metastatic disease during follow-up[1,10,11]. Even with the application of sentinel node biopsy, 6% to 9% of the occult nodal metastases still remain undetected[12,13]. The presence of neck nodal metastases is a crucial prognostic determinant for the patient's survival[14]. As long as novel techniques, such as gene expression profiling or the determination of chromosomal instability in resection margins, are not yet broadly introduced in routine clinical practice[6,15], histologic parameters are still helpful in deciding on the management of the neck. Parameters known to be associated with the presence of regional metastases are infiltration depth of the primary tumor, presence of perineural growth (PG), vascular invasive growth (VG), and infiltrative, noncohesive, growth (IG)[3,16,17]. These "unfavorable" parameters are usually determined only on the definite resection specimen. Knowledge of these parameters in advance could contribute to personalized treatment planning and prevent metastatic growth. The aims of this retrospective study were to evaluate whether the presence or absence of these histologic parameters in the preoperative biopsy correlated with the subsequent resection specimen and to compare the presence of these parameters between lymph node–positive and lymph node–negative patients.

Materials and methods

Patients

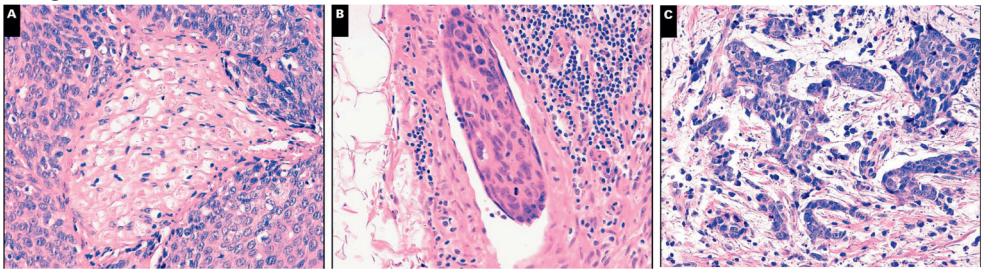
A retrospective chart review was conducted on 226 consecutive patients with a cN0 early stage (pT1-2) OSCC of the tongue, floor of mouth, or cheek (International Classification of Diseases for Oncology, 3rd Edition, locations C02.0–C02.3, C04, and C06.0)[18] who were treated with a primary surgical resection with or without a selective neck dissection at the Department of Oral and Maxillofacial Surgery of the University Medical Center Utrecht between 2004 and 2010. All patients were staged and treated according to the guidelines of the Dutch Society of Head and Neck Cancer[19]. Twenty-one patients were excluded because of a previous head and neck malignancy within the past 5 years, 39 patients because a preoperative biopsy was not available, and 17 patients due to insufficient quality of the biopsy specimen to assess all three histologic parameters. Patients were followed up for 3 years postoperatively. Patients with a pathologic positive neck after a neck dissection and

those who were confronted with neck nodal metastases during follow-up were classified as “node positive” (N+). All others were classified as “node negative” (N–).

Pathologic analysis

All included preoperative biopsy specimens were taken randomly. A defined protocol on size, volume, or location of the biopsy specimen did not exist. Based on the histologic diagnosis, four experienced head and neck surgeons performed the tumor resections with macroscopic safety margins of at least 10 mm. Gross diameter and thickness of the biopsy specimen as well as the actual tumor size in millimeters were collected when present. Of every neck dissection specimen, the presence of metastases was determined manually. Nodes were examined by cutting every node in half, not by stepped serial sectioning or immunohistochemistry. The location was pointed out by the level system described by Robbins et al[20]. The preoperative biopsy and surgical resection specimens of the primary tumors were all reassessed by an experienced head and neck pathologist (S.M.W.) who was blinded for the correlation of histologic parameters between biopsy and resection specimens. The presence or absence of PG, VG, and IG was determined on both the biopsy and corresponding resection specimens (Image 1). PG was defined as the presence of malignant cells in the neural space and/or the movement of malignant cells along the nerve[21]. VG was defined as the presence of aggregates of tumor cells within endothelial-lined channels or invasion of the media of a vessel with ulceration of the intima. IG was defined based on the presence of noncohesive tumor cells that form an ill-defined edge with formation of strands with or without isolated tumor islands[22]. Comparison of histologic parameters between biopsy and resection specimens of one patient was regarded as one case.

Image 1.



A, Perineural growth: tumor cells completely surrounding a nerve and invading its perineurium (H&E, ×200). **B**, Vascular invasive growth: capillary filled by a rounded islet of tumor cells (H&E, ×200). **C**, Infiltrative (noncohesive) growth: invasive squamous cell carcinoma consisting of very irregular tumor islets with spidery protrusions into the surrounding desmoplastic stroma (H&E, ×200).

Statistical analysis

Of every histologic parameter, its prevalence (P), diagnostic accuracy (point estimate and 95% confidence interval [CI]), and the positive and negative "diagnostic gain" of the histologic parameters were determined. The diagnostic accuracy comprises sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity (or true-positive rate) is defined in this case as the probability of having a positive test (biopsy) given that the histologic parameter is present in the resection specimen, whereas specificity (or true-negative rate) is the probability of a negative test if the parameter is truly absent in the resection specimen. PPV is defined as the probability of actually having the parameter in those with a positive test. The probability of not having the parameter in those with a negative test is given by the NPV [23]. The positive and negative diagnostic gains (G+ and G–) were calculated to reflect the increase in information derived from the test. G+ expresses the increase from pretest probability to posttest probability if the test result is positive (G+ = P – PPV). G– gives the drop of pretest probability to posttest probability when the test is negative (G– = P – [1 – NPV]) [23]. To calculate these results, the histologic parameter in the resection specimen was used as the reference standard. Prevalence was taken as the pretest probability.

The gross thickness of the biopsy specimen was related to the corresponding tumor thickness. The predictability of histologic parameters was related to the gross diameter of the biopsy specimen. The histologic parameters found in the resection specimen and biopsy specimen were related to the N status and survival. Hypothesis testing of categorical data was done with the Fisher exact test. The Mann-Whitney U test was used for calculation of P values of continuous variables that were not normally distributed. Using life table techniques, overall survival (OS) rates were calculated, illustrated by Kaplan-Meier plots. OS was calculated from date of diagnosis to date of death from any cause. For disease-specific survival (DSS), censoring occurred at date of death from causes other than OSCC or at the end of follow-up, whichever came first. Covariates were compared with the log-rank test. Median follow-up duration was 57 months (interquartile range, 38–76). All test statistics were two-tailed, and the significance level was set at $P < .05$. Statistical analyses were performed with Stata statistical software (Release 12; StataCorp LP, College Station, TX) and Statistical Package for the Social Sciences (SPSS for Mac, release 22.0.0.0; SPSS, Chicago, IL).

Results

Patient characteristics

In total, 149 patients were enrolled in the present study. The majority had a T1 tumor (63%), and most tumors were located on the tongue (51%). See Table 1 for the other patient characteristics.

Table 1. Patient characteristics (n = 149)[a]

Characteristic	Value
Sex	
Male	87 (58)
Female	62 (42)
Age, mean ± SD, y	63 ± 12
Site	
Tongue	76 (51)
Floor of mouth	59 (40)
Cheek	14 (9)
T stage	
T1	94 (63)
T2	55 (37)
N stage	
N+	33 (22)
N–	116 (78)

N+, patients with occult metastasis; N–, patients without occult metastasis.

[a] Values are presented as number (%) unless otherwise indicated.

Histologic growth parameters related to N stage and survival

Thirty-three (22%) patients with early OSCC had or developed neck nodal disease (N+). In these N+ patients, PG, VG, and IG were significantly more often present in the resection specimen compared with N− patients (PG, 42% vs 22%, P = .02; VG, 27% vs 5%, P = .001; and IG, 85% vs 54%, P = .001) Table 2. However, biopsy specimens without any unfavorable parameter compared with biopsy specimens with one growth parameter and two or more unfavorable parameters showed no significant differences concerning N status (P = .16 and P = .29, respectively) Table 3. OS and DSS were also not significantly different between these three groups (P = .59 and P = .45, respectively).

Table 2. histologic parameters in resection specimen in relation to N stage[a]

Characteristic	N– (n = 116)	N+ (n = 33)	*P* Value
Tumor thickness, median (interquartile range), mm	5 (2-8)	9 (4-14)	<.001[b]
Perineural growth	25 (22)	14 (42)	.02[c]
Vascular invasive growth	6 (5)	9 (27)	.001[c]
Infiltrative growth	63 (54)	28 (85)	.001[c]

N+, patients with occult metastasis; N–, patients without occult metastasis.

[a] Values are presented as number (%) unless otherwise indicated.

[b] Mann-Whitney U test.

[c] Fisher exact test.

Table 3. histologic parameters in biopsy specimen in relation to N status (n = 149)[a]

Variable	Biopsy –[b] (n = 67)	Biopsy 1[c] (n = 76)	Biopsy ≥2[d] (n = 6)
N stage			
N+	11 (16)	20 (26)	2 (33)
N–	56 (84)	56 (74)	4 (67)
Growth parameter			
Perineural growth	0	1 (1)	5 (83)
Vascular invasive growth	0	1 (1)	1 (17)
Infiltrative growth	0	74 (97)	6 (100)

N+, patients with occult metastasis; N–, patients without occult metastasis.

[a] Values are presented as number (%) unless otherwise indicated

[b] Biopsy negative for unfavorable histologic parameters.

[c] Biopsy positive for one unfavorable histologic parameter.

[d] Biopsy positive for two or more unfavorable histologic parameters

Histologic correlation between biopsy and definite resection specimens

Perineural Growth

PG was present in 26% (95% CI, 19%–34%) of the resection specimens Table 4. A similar result (ie, PG in the biopsy specimen and in the subsequent resection specimen) was obtained in 114 (77%) cases—a false-negative result in 34 (24%) of 143 negative cases and a false-positive result in one (17%) of six positive cases. The probability of having PG in the definite resection specimen increased from 26% to 83% when it was already present in the biopsy specimen. The absence of PG in the biopsy specimen reduced the probability of PG in the resection specimen by 2% (Table 4) Figure 1.

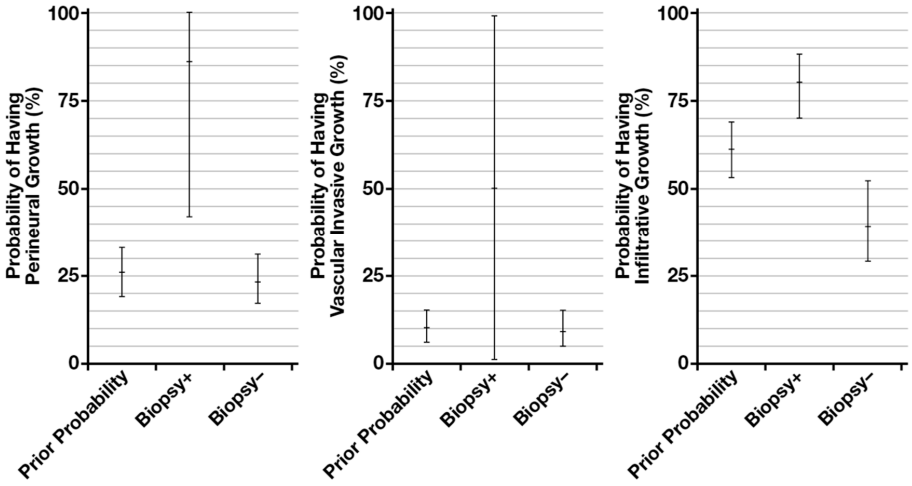
Table 4. Correlation of histologic growth parameters between diagnostic biopsy and subsequent resection specimens [a]

	Perineural Growth	Vascular Invasive Growth	Infiltrative Growth
Prevalence	0.26 (0.19-0.34)	0.10 (0.06-0.16)	0.61 (0.53-0.69)
Sensitivity	0.13 (0.04-0.27)	0.07 (0.00-0.32)	0.70 (0.60-0.79)
PPV	0.83 (0.36-1.00)	0.50 (0.01-0.99)	0.80 (0.70-0.88)
NPV	0.76 (0.68-0.83)	0.90 (0.85-0.95)	0.61 (0.48-0.72)
G+	0.57	0.40	0.19
G–	0.02	0.00	0.22

G+, positive diagnostic gain; G-, negative diagnostic gain; NPV, negative predictive value; PPV, positive predictive value.

[a]Values are presented as fractions (95% confidence interval)

Figure 1. Probability of having a specific growth pattern in relation to biopsy status.



Vascular invasive Growth

The prevalence of VG was 10% (95% CI, 6%–16%). A similar result was obtained in 134 (90%) cases—a false-negative result in 14 (10%) of 147 negative cases and a false-positive result in one (50%) of two positive cases. The probability of having VG in the definite resection specimen increased from 10% to 50% when it was already present in the biopsy specimen. Absence of VG in the diagnostic biopsy specimen did not change the probability of VG in the resection specimen
(Table 4 and Figure 1).

Infiltrative Growth

In 61% of the resection specimens, IG was present (95% CI, 53%–69%). A similar result was obtained in 106 (71%) cases—a false-negative result in 27 (39%) of 69 negative cases and a false-positive result in 16 (20%) of 80 positive cases. The probability of having IG in the definite resection specimen increased from 61% to 80% when it was already present in the biopsy specimen. When IG was absent in the biopsy specimen, the probability of having IG in the resection specimen was reduced by 22% (Table 4 and Figure 1).

Biopsy specimen thickness in relation to tumor thickness

Details on gross biopsy specimen thickness were present in 41 patients. Mean (SD) thickness of these 41 biopsy specimens was 3.9 (1.6) mm, and mean (SD) thickness of the corresponding tumors was 8.4 (5.9) mm. In seven (17%) patients, biopsy specimen thickness was the same as tumor thickness. In 28 (68%) patients, tumor thickness exceeded the thickness of the biopsy specimen, and in six (15%) patients, the thickness of the biopsy specimen was higher than the tumor thickness.

Biopsy specimen diameter in relation to tumor diameter and predictability of growth parameters

Details on gross biopsy specimen diameter were present in 68 patients. The mean (SD) diameter of 68 biopsy specimens was 8.2 (3.5) mm, and the corresponding tumors had a mean (SD) diameter of 18.9 (9.6) mm. In 39 (57%) cases, biopsy specimen diameter was more than two times as low as the corresponding tumor diameter. Presence or absence of growth parameters was correctly predicted in 10 (26%) of these cases. In the other 29 patients, in whom the biopsy specimen diameter was more than half of the tumor diameter, growth parameters were significantly more often correctly predicted (52%; P = .03).

Discussion

Preoperative assessment of histologic parameters is crucial for clinical decision making in various oncologic specialties. In urologic, colorectal, and gynecologic cancers, histologic characteristics guide further treatment[24-28]. In head and neck cancers, tumor diameter, thickness, and nodal spread are the most important determinants for therapy[14]. Increasing tumor infiltration depth is positively associated with neck nodal metastasis[3]. Analysis of biopsy specimen thickness compared with the corresponding tumor thickness revealed that most biopsy specimens did not exceed the actual tumor thickness. In only 15% of the cases, the biopsy specimen was thicker and could give reliable information about the actual infiltration depth. It is known, however, that the presence of PG, VG, and IG in the resection specimen is positively associated with nodal involvement[29-32]. Our data show a similar trend.

All assessed histologic parameters are significantly more often present in lymph node–positive patients. Reliable preoperative knowledge of these unfavorable parameters can be of utmost importance for further patient-specific treatment planning of the cN0 neck. To our knowledge, the correlation between the presence of histologic growth parameters in the preoperative biopsy specimen and definite resection specimen has not been analyzed. Consequently, evidence-based information about the value of the determination of histologic parameters in incisional biopsy specimens is missing. In our study, the prevalence of PG, VG, and IG was 26%, 10%, and 61%, respectively. Although the prevalence of these parameters varies in literature, the distribution was similar, as reported by other authors[14,17,33,34]. The wide variation in percentages reported in the literature could be explained by interobserver variability, a known phenomenon in histologic assessment of these parameters[35,36].

Overall, the results show a poor correlation between incisional biopsy and resection specimens with respect to VG, PG, and IG. Occult nodal metastases were present in a high proportion of patients with biopsy specimens negative for PG, VG, and IG. Therefore, presence or absence of these unfavorable histologic parameters in the preoperative biopsy specimen holds little diagnostic information for the nodal status. Subsequently, no significant difference in OS and DSS was seen between these patient groups. A possible explanation for the poor correlation could be the small amount of tissue taken during incisional biopsies, since for most clinician's pathologic confirmation of only the diagnosis of OSCC is sufficient for further treatment planning. Fragments of tissue can provide enough information for the histologic diagnosis of OSCC but might lead to difficulties in the determination of specific parameters such as PG, VG, and IG[37,38]. Our data also showed that biopsy specimens with a diameter more than half the actual tumor diameter are significantly more likely to correctly identify the presence or absence of growth parameters. To date, no randomized controlled clinical trials are available that have assessed the required minimal biopsy specimen volume for a reliable determination of these histologic parameters. Another explanation is the specific origin of the biopsy specimen, which can possibly affect the presence of histologic parameters. Studies have shown that biopsy specimens taken from the tumor center provide different information compared with specimens of the tumor front[39,40]. It is assumed that the most informative part of the tumor character will be found at the tumor front[39]. Geographical intratumor heterogeneity is already a known phenomenon in other malignancies such as breast, prostate, and colorectal cancer[41-43]. Also, in OSCC, there is evidence for intratumor heterogeneity[44-46] that could explain the poor correlation between biopsy and resection specimens. Of all biopsy specimens included in our study, little information was available regarding the precise location of the biopsy specimen taken (i.e. border or center of the tumor). A protocolled manner of performing an incisional biopsy (i.e. at the border of the tumor), with a minimum amount of tissue and sufficient thickness (i.e. including muscle), as advised by others[37,38], might provide a better correlation between biopsy and resection specimens.

Since morbidity, survival, and quality of life are increasingly relevant aspects of decision making for therapeutic intervention in patients with cancer (patient-specific therapy), new treatment algorithms must be explored. Especially in early stage oral cancers, there is an ongoing debate about how to deal with the cN0 neck since imaging does not sufficiently display early metastatic spread[4,47,48]. There is no doubt about the need to demonstrate occult nodal disease more accurately. New analytic methods, such as fluorescence in situ hybridization for the detection of chromosome instability in resection margins or gene expression profiling and next-generation sequencing, are promising diagnostic tools leading to personalized treatment plans[6,15,49-51]. For the time being, however, determination of the histologic parameters in incisional biopsy specimens could bridge the gap between unsatisfactory imaging results and the problem of over- or undertreatment in patients with cN0 necks.

In this retrospective study, the histologic parameters PG, VG, and IG found in biopsy specimens were poorly correlated with the subsequent resection specimen. Especially the absence of PG and VG in the biopsy specimens was not representative of the subsequent resection specimen and the subsequent risk of regional metastases. Our future concern will therefore focus on a protocolled way of taking biopsy specimens to facilitate decision making in the treatment of early OSCC. In conclusion, tumor thickness, PG, VG, and IG are associated with regional metastases in patients with OSCC. Unfavorable histologic parameters in preoperative biopsy specimens showed poor correlation with the subsequent resection specimen. Especially biopsy specimens without PG and VG were not representative of the resection specimen and the subsequent risk of having occult metastasis.

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3

CHAPTER THREE

The value of histological grading of biopsy and resection specimen in early stage oral squamous cell carcinomas

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ABSTRACT

Introduction In oral squamous cell carcinoma (OSCC) the differentiation grade of the tumor is determined on the biopsy and the resection specimen. The relation between tumor grade, nodal metastasis and survival is debatable. The aims of this study were to determine the correlation between differentiation grade of the biopsy and the resection specimen. Furthermore, we wanted to correlate tumor differentiation grade with nodal stage and survival.

Patients and methods One-hundred and forty-five patients with OSCC staged as T1-2, N0 of the tongue, floor of mouth or cheek with primary resection of the tumor were examined. Biopsy and resection specimen were histologically re-assessed with regard to differentiation grade, as well as infiltrative, perineural and vascular invasive growth.

Results This study showed a poor correlation between differentiation grade in the incisional biopsy and the resection specimen of the same tumor. No significant relation between differentiation grade of the resection specimen and nodal involvement, as well as overall and disease-specific survival was found.

Conclusion In early OSCC the differentiation grade determined by biopsy is of little predictive value for the grading of the resection specimen. Poor differentiation grade could not be related to the presence of nodal metastasis or survival and seems not to have any prognostic value concerning outcome. Treatment planning must be related to these findings.

Introduction

In early stage, stage (I-II) oral squamous cell carcinoma (OSCC) complete surgical removal of the tumor is the treatment of choice[1]. The management of the clinically negative neck (cN0) is still an issue of debate[2-8]. The presence of histological features, such as perineural growth and vascular invasive growth and infiltrative growth is associated with an increased risk of nodal metastases[4,9,10]. In some studies, moderate and poor differentiation grade of the OSCC is correlated with a more aggressive tumor behavior and subsequent risk of regional nodal metastases[11,12]. Others did not find this association between grade and nodal status[13,14]. In many head and neck cancer centers, differentiation grade is routinely determined on the biopsy and resection specimen. It is unknown whether the differentiation grade of the preoperative biopsy specimen corresponds to the grade of the subsequent resection specimen and could play a role in the decision making how to treat the neck. The aims of this study were to determine the correlation between differentiation grade of the biopsy and resection specimen in stage I and II OSCC's. Furthermore, we aimed to correlate differentiation grade of the resection specimen with other growth parameters, nodal stage and survival

Materials and methods

Patients

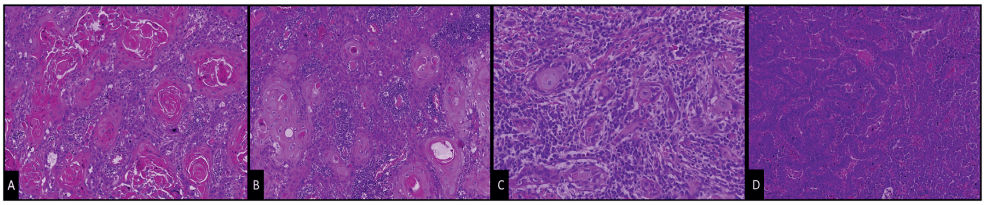
The prospectively collected database of the Department of Oral and Maxillofacial Surgery of the University Medical Centre Utrecht was queried to identify patients with a pT1-2 cN0, OSCC of the tongue, floor of mouth or cheek (International Classification of Diseases for Oncology. 3rd Edition locations C02.0-C02.3, C04, and C06.0)[15] All patients were staged and treated according to the guideline of the Dutch Society of Head and Neck Cancer and the UICC TNM staging system[15]. Patients were treated with primary surgical resection with or without a selective neck dissection between 2004 and 2010. To be included in the study, an incisional biopsy had to be taken before the definitive resection with 10mm safety margin was performed and histological paraffin sections of all included biopsies had to be present for re-assessment. In total, 226 patients were identified. Twenty-one patients were excluded because of a previous head and neck malignancy in the last five years, 39 patients because a preoperative biopsy was taken elsewhere and not available for reassessment, ten patients due to the inability to assess differentiation grade of the biopsy specimen, and eleven because the resection specimen showed only micro-invasive growth. Postoperatively, all patients were followed up for at least three years with clinical examination (i.e. palpation of the neck) and on indication US examination accompanied by fine needle aspiration cytology if needed.

Patients were classified as “node-positive” (N+) if a neck dissection was performed and showed a positive node or if a watchful waiting policy of the neck was performed and the patient was confronted with a nodal metastasis during follow-up. All others were classified as “node-negative” (N-).

Histological analysis

All preoperative biopsies were taken randomly. A defined protocol on size, volume or location of the biopsy did not exist. Four experienced head and neck surgeons performed tumor resections with macroscopic safety margins of at least 10mm. The incisional biopsies and surgical resection specimens of the primary tumors were all re-assessed by an experienced head and neck pathologist (SMW) who was blinded for the correlation of histological grade between biopsy and resection specimen. Tumor differentiation grade was determined according to the World Health Organization (WHO) classification system (Broders' grade)[16] based on the differentiation of the cells. Tumors were scored as well differentiated (< 25% of undifferentiated cells), moderately differentiated, (≥25% <50%) poorly differentiated (≥50% < 75%), or undifferentiated (≥75%) (see Figure.1)[17,18].

Figure 1. Differentiation grades in oral squamous cell carcinoma



Legend

A Well differentiated (H&E x 200)
B Moderately differentiated (H&E x 200)
C Poorly differentiated (H&E x 200)
D Undifferentiated (H&E x 200)

Unfavorable growth parameters such as perineural growth, vascular invasive growth and infiltrative growth were all re-assessed on biopsy and resection specimen by the same blinded pathologist (SMW) Perineural growth was defined as the presence of malignant cells in the neural space and/or the movement of malignant cells along the nerve[19]. Vascular invasive growth was defined as the presence of aggregates of tumor cells within endothelial-lined channels or invasion of the media of a vessel with ulceration of the intima.

Infiltrative growth was defined based on the presence of non-cohesive tumor cells that form an ill-defined edge with formation of strands with or without isolated tumor islands[14]. The results found in the resection specimen were regarded as the true pathological diagnosis.

Statistical analysis

Diagnostic accuracy of the biopsy comprises sensitivity, specificity and positive predictive value (PPV). Sensitivity (or true positive rate) was defined as the probability of having a positive test, i.e. the finding of a certain differentiation grade in the biopsy, given this specific differentiation grade is present in the resection specimen. Specificity (or true negative rate) is the probability of absence of a particular differentiation grade in the biopsy if the parameter was truly absent in the resection specimen. PPV is defined as the probability of actually having the parameter in those with a certain differentiation grade[20]. To calculate these results, the histological parameter in the resection specimen was used as reference standard. P was taken as the pre-test probability. Differentiation grade in the resection and biopsy specimen was related to N status. Tumor grade in the resection specimen was correlated with unfavorable histological growth parameters (i.e. perineural growth, vascular invasive growth and infiltrative growth) and survival. Hypothesis testing of categorical data was done with Fisher's exact test. Using life table techniques, overall survival and disease-specific survival rates were calculated, illustrated by Kaplan-Meier plots. Overall survival was calculated from date of diagnosis to date of death from any cause. For disease-specific survival, censoring occurred at date of death from causes other than OSCC or at the end of follow-up, whichever came first. Covariates were compared with the log-rank test. Of every histological parameter, prevalence (P) and diagnostic accuracy (point estimate and 95% confidence interval), was determined. All test statistics were two tailed, and the significance level was set at $p < 0.05$. Analyses were performed with Statistical Package for the Social Sciences (SPSS for Mac, release 22.0.0.0, 2013, SPSS Inc.)

Results

Patient characteristics

In total, 145 patients were included in this study. Table 1 shows the patient characteristics. The majority (60%) of patients had a pT1 tumor, which was located on the tongue in 53%. More than half of all tumors was moderately differentiated, i.e. 78% of the biopsy specimens and 75% of the resection specimens. In the resection specimens, 15% of the tumors was classified as well differentiated, 8% as poorly differentiated and 2% as undifferentiated.

Table 1. Patient characteristics [a] (n=145)

Characteristic	
Gender	
Male	81 (56)
Female	64 (44)
Age – years	
Mean (SD)	63 (12)
Site	
Tongue	77 (53)
Floor of mouth	52 (36)
Cheek	16 (11)
T stage	
T1	87 (60)
T2	58 (40)
N Stage	
N+	41 (28)
N-	104 (72)

[a] *Values are presented as number (%)*

N+: patients with occult metastasis

N-: patients without occult metastasis

Histological correlation between preoperative biopsy and resection specimen

Well differentiated

Fourteen tumors (10%) were graded as well differentiated on biopsies. The prevalence of well differentiated tumors was 15% (95% confidence interval (CI), 9%-22%) based on the resection specimen. A similar result between biopsy and resection specimen was obtained in six cases (43%), a false-positive result was found in eight cases (57%). Of the well differentiated tumors in biopsies, seven (50%) of the resection specimens were eventually classified as moderately and one (7%) as poorly differentiated (Figure 2). The probability of the tumor being well differentiated increased with 28% when the biopsy was scored as well differentiated (Table 2 and Figure 2).

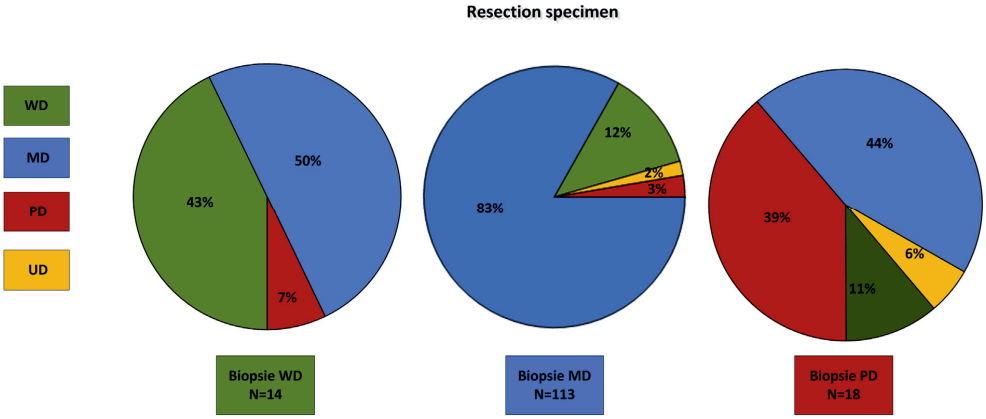
Moderately differentiated

One-hundred-thirteen tumors (78%) were graded as moderately differentiated on biopsies. The prevalence of moderately differentiated tumors was 75% (95% CI, 67%-82%). on the resection specimen. In 94 cases (83%), biopsy and resection specimen were both classified as moderately differentiated. A false-positive result was found in nineteen cases (17%). Of the moderately differentiated biopsies, fourteen (12%) of the resection specimens were eventually classified as well differentiated, three (3%) poorly differentiated and two (2%) as undifferentiated. The probability of the tumor being moderately differentiated increased from 75% to 83% when this histological grade was seen in the preoperative biopsy (Table 2 and Figure 2).

Poorly differentiated

Eighteen tumors (12%) were graded as poorly differentiated on biopsies. Eight percent (95% CI, 4%-13%) of all the tumors were poorly differentiated on the resection specimen. A similar result between biopsy and resection specimen was obtained in seven cases (39%), a false-positive result in eleven cases (61%). Of the poorly differentiated biopsies, two (11%) were eventually classified as well differentiated, eight (44%) as moderately differentiated, and one (6%) as undifferentiated on the resection specimen. The probability of having a poorly differentiated tumor increased from 8% to 39% when the biopsy was classified as poorly differentiated (Table 2 and Figure 2)

Figure 2. Differentiation grade of biopsy specimen compared to resection specimen



Legend
WD Well Differentiated
MD Moderately Differentiated
PD Poorly Differentiated
UD Undifferentiated

The circles represent the distribution of differentiation grades in the resection specimen when the biopsy has a certain differentiation grade

Table 2. Correlation of tumor differentiation grade between diagnostic biopsy and subsequent resection specimen[a]

	Well differentiated (95%CI)	Moderately differentiated (95%CI)	Poorly differentiated (95%CI)
Prevalence	0.15 (0.09-0.22)	0.75 (0.67-0.82)	0.08 (0.04-0.13)
Sensitivity	0.27 (0.11-0.50)	0.86 (0.78-0.92)	0.64 (0.31-0.89)
Specificity	0.94 (0.88-0.97)	0.47 (0.30-0.65)	0.92 (0.86-0.96)
Positive predictive value	0.43 (0.18-0.71)	0.83 (0.75-0.90)	0.39 (0.17-0.64)
Positive diagnostic gain	0.28	0.08	0.31

[a] *Values are presented as fractions (95% confidence intervals)*

Differentiation grade related to N stage and survival

Forty-one (28%) patients with early OSCC had or developed neck nodal disease (N+). No significant difference was seen between differentiation grade of the biopsy or resection specimen and N status (p = 1.0 and p = 0.50, respectively) (see Table 3). Overall survival and disease-specific survival were not significantly different in patients with well, moderately or poorly differentiated tumors in the resection specimen *(p* = 0.65 *and p* =0.44).

Table 3. Differentiation grade of resection and biopsy specimen in relation to N status[a]

Characteristic	N- (n=104)	N+ (n=41)
Resection specimen		
Well differentiated	16 (15)	6 (15)
Moderately differentiated	79 (76)	30 (73)
Poorly differentiated	6 (6)	5 (12)
Undifferentiated	3 (3)	0 (0)
Biopsy specimen		
Well differentiated	10 (10)	4 (10)
Moderately differentiated	81 (78)	32 (78)
Poorly differentiated	13 (13)	5 (12)

[a] *Values are presented as number (%)*
N+: patients with occult metastasis
N-: patients without occult metastasis

Differentiation grade in resection specimen related to unfavorable growth parameters

Resection specimens with a poorly differentiated tumor showed a significantly higher amount of vascular invasive growth compared to moderately differentiated tumors (p = 0.02). No differences were seen between differentiation grade and perineural or infiltrative growth (p = 0.15 and p = *0.85*, respectively) (see Table 4).

Table 4. Differentiation grade of resection specimen in relation to growth parameters[a]

Growth parameter	Well Differentiated (n=22)	Moderately Differentiated (n=109)	Poorly Differentiated (n=11)	Undifferentiated (n=3)	P value
Peri-neural	3 (14)	33 (30)	5 (46)	0 (0)	0.15
Vascular invasive	2 (9)	9 (8)	4 (36)	0 (0)	0.07
Infiltrative	15 (68)	70 (64)	8 (72)	2 (67)	0.85

a Values are presented as number (%)
N+: patients with occult metastasis
N-: patients without occult metastasis

Differentiation grade combined with infiltrative growth pattern in relation to N status

Patients with moderately differentiated, infiltrative growing tumors were more often node positive than moderately differentiated tumors with a cohesive growth pattern (p = 0.02). No significant differences were seen in nodal status within well or poorly differentiated tumors with an infiltrative or cohesive growth pattern. (see Table 5)

Table 5. Differentiation grade of resection combined with infiltrative growth pattern in relation to N status[a]

Characteristic	N+ (n=104)	N- (n=41)	P value
WD & IG+	5 (33)	10 (67)	0.62
WD & IG-	1 (14)	6 (86)	
MD & IG+	24 (34)	46 (66)	0.02
MD & IG-	5 (13)	33 (87)	
PD & IG+	4 (50)	4 (50)	0.47
PD & IG-	0 (0)	2 (100)	

[a]*Values are presented as number (%)*
N+: patients with occult metastasis, N-: patients without occult metastasis
WD: Well Differentiated, MD: Moderately Differentiated, PD: Poorly Differentiated
IG+: infiltrative growth pattern, IG-: cohesive growth pattern

Discussion

The majority of early OSCC in this study was moderately differentiated (75%), while 15% were well differentiated, 8% poorly differentiated, and 2% undifferentiated. In literature the prevalence of these key growth determinants varies widely[10,21,22]. The difference in the results published in literature can partly be explained by inter-observer variability, a well-known phenomenon in histological assessment of resection specimens[23-25]. The subjective nature of the grading system leaves room for a wide variability and may explain the inaccuracy and poor correlation with nodal status and survival[11]. Because of the lack of valid alternatives many head and neck centers routinely grade OSCC on biopsy and resection specimens. This study showed a poor correlation between the differentiation grade found in the incisional biopsy and the resection specimens of the tumor. In cases of well or poorly differentiated tumors on biopsy the PPV was disappointing with over half of the cases rated differently. The relatively good PPV of moderately differentiated tumors on biopsy was also due to the high prevalence of moderately differentiated tumors on resection specimens, which increased the chance of a matching biopsy. This is probably also the reason that the majority of the incorrectly scored well and poorly differentiated biopsies were in fact moderately differentiated. An explanation for the overall poor correlation could be intra-observer variability[23-25]. In other diagnostic fields of medicine (i.e. radiology) intra- and inter-observer variability is an important factor in deciding, whether a diagnostic tool is reliable for the application in patient care or not[26]. Validation, definition making and training in interpretation of images can lead to a better intra- and inter-observer agreement[27]. Another explanation could be the insufficient amount of tissue taken during the incisional biopsy, as for clinicians the pathological confirmation of OSCC is in most cases sufficient for further treatment planning. Fragments of tissue can provide enough information for the pathological diagnosis of OSCC but may lead to difficulties in the determination of the differentiation grade[9,28,29]. In an earlier study on small OSCC we could show that biopsies with a diameter more than half of the actual resection specimen are more likely to correctly identify pathological growth characteristics[9]. To date, no randomized controlled clinical trials are available that have assessed the required minimal biopsy volume for a reliable determination of histological parameters. The specific origin of the biopsy can possibly affect the differentiation grade. Studies have shown that a biopsy taken from the tumor center provides different information compared to the tumor front[30,31]. This locational intra-tumor heterogeneity is already a known phenomenon in other malignancies as breast, prostate and colorectal cancer[32-34]. Although OSCC is a different type of cancer there is also evidence for intra-tumor heterogeneity[12,35,36] which might be another explanation for the poor correlation between biopsy and resection specimen[11,12]. A defined protocol in minimal size, volume and location of the biopsies could positively influence the correlation between biopsy and resection specimen.

Pre-operative assessment of more specific histological characteristics can be of importance in clinical decision making in cancer treatment. The Gleason score in prostate cancer biopsies e.g. is a good example in pre-operative grading[37,38]. Also for breast and cervical cancer, pre-operative grading can guide further treatment[39-41]. For head and neck cancer, Broder's (WHO) grading classification is popular, because it is relatively simple and pathologists are familiar with it[11,29]. However, several authors stated that Broder's grade shows only poor correlation with outcome[13,14]. Other studies showed that a deterioration of differentiation grade was positively associated with nodal involvement and therefore could play a role in the decision whether or not to treat the cN0 neck in small OSCC[11,12,42]. Pathological observations used for treatment planning should be biologically meaningful and reproducible from one pathologist to another to have substantial validity[24]. In our study no significant relation between differentiation grade of the resection specimen and nodal involvement could be demonstrated. Also, in overall and disease-specific survival no significant difference was seen in relation to different differentiation grades. This suggests that deterioration of the differentiation grade of the tumor is not independently related to outcome[13,14]. It is recommended to add the pattern of invasion, i.e. cohesive versus infiltrative growth, to the grading system to create a more representative and complete prediction of the tumor's behavior[28,29]. In this study, moderately differentiated tumors with an infiltrative growth pattern showed more nodal metastases. This could not be demonstrated in poorly and well-differentiated tumors, probably because the numbers are too small to reach significance. The most likely explanation, however, is that the presence of infiltrative growth could be regarded as an independent risk factor for nodal metastasis apart from differentiation grade[1,9]. Still, different authors assume that poorly differentiated tumors have a more aggressive growth behavior[11,12,42]. Poorly differentiated tumors were more often vascular invasive, which is associated with poor prognosis, than moderately differentiated tumors[22]. No correlation was found between any other unfavorable growth parameter such as perineural and vascular invasive growth.

Conclusion

differentiation grade determined by biopsy showed only poor correlation with the resection specimen and is therefore of little predictive value. Since deterioration of the differentiation grade could not be related to the presence of nodal metastasis or survival, these criteria don't have any prognostic value concerning outcome. Consequently, these items are of little value for treatment planning. Adding the pattern of invasion to the differentiation grade of resection specimen in small OSCC could increase the prognostic value probably because it is, apart from differentiation grade, an independent risk factor for nodal metastasis.

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4

CHAPTER FOUR

Inter observer variability for pathological growth parameters determined on digital slides in oral squamous cell carcinoma

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ABSTRACT

Introduction In oral squamous cell carcinomas (OSCC) decisions regarding adjuvant treatment are mainly based on pathological parameters i.e. Bony involvement (BI), Infiltrative growth (IG) Vascular invasive growth (VG) and Perineural growth (PG). Pathological assessment is more and more done on digital slides and should be reproducible from one pathologist to the other to have substantial validity. The aim of this study was to assess the IOV within a group of expert head and neck pathologists in the Netherlands.

Patients and Methods Thirty-three digitized H&E sections of 33 OSCC's where included. Six head and neck pathologists of six different Dutch head and neck cancer centers re-assessed the presence or absence of BI, IG, VG and PG. To assess the IOV between the six pathologists the Fleiss' kappa was calculated.

Results For BI IG and PG the Fleiss' Kappa's where resp. 0.457 ($p<0.001$), 0.100 ($p<0.001$), 0.223 ($p<0.001$) for overall agreement.

Conclusion With at most a moderate agreement in case of digital examination of H&E slides, current reproducibility is not reliable enough cannot be used to guide adjuvant treatment planning in daily clinical practice. Clear and transparent definitions in quality of screens and screen settings as well as establishing clear definitions for the different histological parameters by regular consensus meetings may contribute to a better reproducibility.

Introduction

Oral squamous cell carcinoma (OSCC) is preferably treated by complete surgical removal and its local recurrence is an important prognostic factor for survival[1-3]. Based on the histopathology report of the resection specimen, adjuvant treatment may consist of additional surgery, postoperative radiotherapy (PORT) or PORT in combination with systemic treatment, i.e. chemo-radiation. All adjuvant treatment modalities add to the total of overall adverse effects, such as functional impairment after re-resection or early and late radiation toxicity after PORT[4-6]. Moreover, adjuvant PORT may hamper future treatment of second primary OSCC's that occur in approximately 20% of these patients. Histopathological tumor characteristics of the primary tumor, such as margin status, bone invasion (BI) and the presence of "unfavorable" growth parameters of the tumor front i.e. spidery non-cohesive infiltrative growth pattern (IG) vascular invasive Growth (VG) and perineural growth (PG) are important prognostic factors for the risk on local and regional recurrence[1, 7-9]. Subsequently, clinical decisions regarding adjuvant treatment are mainly based on the scoring of these parameters. Nowadays these parameters are increasingly scored on digitized slides. To have substantial validity, pathological assessment should be biologically meaningful and reproducible from one pathologist to the other[10]. To our knowledge, no studies are available concerning the inter-observer variability (IOV) of the above mentioned histopathological parameters of OSCC in digitized slides. The aim of this study was to assess such an IOV within a group of expert head and neck pathologists in the Netherlands

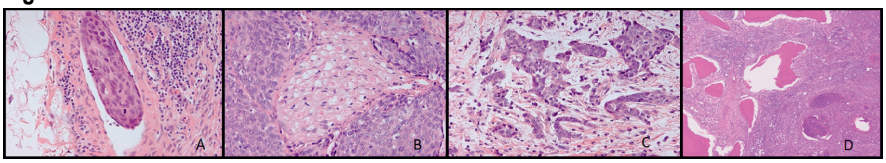
Materials and methods

Six dedicated and experienced head and neck pathologists of six different Dutch head and neck cancer centers participated in this study (SMW, LAS, BvdV, EB, MvdH, SK). Patients with primary OSCC resected between 2009 and 2014 were selected. One representative section for determination of different pathological growth parameters of the tumor was selected by SMW and digitized. The sections were scanned using the Hamamatsu Nanozoomer XR (Hamamatsu Photonics K.K, Hamamatsu, Japan) at 40x with a scan resolution of 0.23 um/pixel and a low JPEG compression (Q=90). The digital slides were then uploaded to an online research digital pathology platform hosted by the University Medical Centre Utrecht (https://tepis.umcutrecht.nl). Every slide was placed in a separate case folder with a distinctive case ID. All pathologists received separate login credentials and had immediate access to all cases. No specific guidelines for screen settings and magnification where provided. In total, 33 digitized H&E sections of 33 tumors where included for examination.

Pathology analysis

All pathologists assessed the 33 digital H&E sections and were instructed to judge all cases as they would in their routine practice, without previous mutual deliberation about the criteria for the histopathological parameters. The presence or absence of BI, IG, VG and PG was determined (Figure 1). Each pathologist noted the outcome on a standardized data entry sheet. All pathologists where blinded to each other's results. Only two members of the study team (EAD, NAI), who did not participate in grading of the slides, had access to all data sheets.

Figure 1



A: Perineural growth: tumor cells completely surrounding a nerve and invading its perineurium (200x)

B: Vascular invasion: capillary filled by a rounded islet of tumor cells (200x)

C: Spidery growth: invasive squamous cell carcinoma consisting of very irregular tumor islets with spidery protrusions into the surrounding desmoplastic stroma (200x).

D: Bony invasion: infiltration of tumor cells through the cortical bone (200X)

Statistical analysis

To assess the inter-rate reliability between the six pathologists the Fleiss' kappa was calculated for bony invasion, infiltrative growth pattern and perineural growth. Fleiss' kappa calculates the degree of agreement between observers over that which would be expected if all observers made their ratings completely randomly. Kappa could not be reliably calculated for vascular invasive growth due to the low amount of cases positive for this prognostic factor[11]. The nomenclature set forth by Landis and Koch was used for the interpretation of the kappa statistics[12]: 0 poor agreement (agreement expected by chance), 0.01–0.2 slight agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 substantial agreement, 0.81–1 almost perfect agreement. For each pathological growth pattern and for having 2 or more unfavorable prognostic factors, the interobserver concordance was calculated between any two observers. Two observers had an interobserver concordance of one hundred percent if they had scored the presence or absence of a specific growth parameter for all thirty-three cases the same. All analyses were performed with Stata Statistical Software (Release 12. College Station, TX: StataCorp LP).

Results

Patient characteristics are listed in Table 1. Patients were mainly male (64%), had a median age of 69 years and a tumor located on the tongue (36%). Seven specimens (21%) contained (a section of) mandibular bone on which BI could be determined.

Table 1 Patient characteristics

Characteristics	N=33
Sex, n(%)	
Male	21 (64)
Female	12 (36)
Age (years)	
Mean (SD)	69 (12)
Range	27-88
Primary tumor site, n(%)	
Tongue	12 (36)
Floor of mouth	6 (18)
Gum Lower Jaw	3 (9)
Gum Upper Jaw	1 (3)
Mucosa Lower lip	1 (3)
Cheek	5 (15)
Other	5 (15)
clinical T- stage (TNM 7th ed) n(%)	
cT1	9 (27)
cT2	15 (45)
cT3	2 (6)
cT4a	6 (18)
cT4b	1 (3)

For BI the inter observer concordance between the 6 different observers ranged from 73% to 100% with a Fleiss' Kappa of 0.457 ($p<0.001$) for overall agreement. For IG the concordance ranged from 39% to 79% with a Fleiss' Kappa of 0.100 ($p<0.001$) for overall agreement (table 2). For PG the concordance ranged from 33% to 97% with a Fleiss' kappa of 0.223 ($p<0.001$) for overall agreement. Figure 2 a,b,c shows the overall inter-observer agreement for the different growth parameters and figure 2d shows the concordance between observers for having 2 or more unfavorable prognostic factors.

Table 2 inter-observer agreement in determination of BI on 7 digitalized sections and IG and PG on 33 digitized sections

Pathological parameter	Fleiss' kappa	p-value	Degree of agreement
Bony Invasion*	0.475	<0.001	Moderate
Spidery Infiltrative Growth	0.100	<0.001	Slight
Perineural Growth	0.223	<0.001	Fair

**Evaluable on 7 cases*

Figure 2

a: Concordance (%) between observers for bone invasion

Observer	A	B	C	D	E	F
A	-					
B	100	-				
C	91	91	-			
D	100	100	91	-		
E	94	94	91	94	-	
F	82	82	73	82	82	-
Overall	93,4	93,4	87,4	93,4	91	80,2

b: Concordance (%) between observers for infiltrative growth pattern

Observer	A	B	C	D	E	F
A	-					
B	61	-				
C	79	76	-			
D	36	64	52	-		
E	64	61	73	48	-	
F	48	52	39	39	42	-
Overall	57,6	62,8	63,8	47,8	57,6	44

c: Concordance (%) between observers for perineural growth

Observer	A	B	C	D	E	F
A	-					
B	73	-				
C	79	88	-			
D	97	70	76	-		
E	85	64	70	82	-	
F	48	33	39	52	58	-
Overall	76,4	65,6	70,4	75,4	71,8	46

d: Concordance (%) between observers for having two or more negative prognostic factors

Observer	A	B	C	D	E	F
A	-					
B	76	-				
C	76	82	-			
D	76	70	58	-		
E	67	67	61	73	-	
F	58	39	33	70	48	-
Overall	70,6	66,8	62	69,4	63,2	49,6

Concordance (%) between different observers

Discussion

In this cohort, a moderate agreement for BI (kappa 0.475), a fair agreement for PG (kappa 0.223) and only a slight agreement for IG (kappa 0.100) was reached between dedicated pathologists. Although VG is an important prognostic parameter[13]. Reliable information about the IOV of this parameter would be valuable. Unfortunately, we had to leave VG out of analysis because the low number of cases scored positive for VG 5-9/33 and the inability to draw reliable conclusions. In literature a poor IOV in scoring of pathological parameters for head and neck cancer is a well-known phenomenon. For instance, scoring of the pattern of invasion resulted in kappa's between 0.193 and 0.580 which is at most a moderate agreement[14, 15] and determination of differentiation grade of OSCC[10, 16, 17] showed kappa's varying from 0.38 to 0.63 (moderate to substantial)[16, 18]. The pathology report is crucial in deciding whether or not to perform an adjuvant treatment after primary surgery of OSCC. In case of "close margins" there is discussion between clinicians about the necessity of local adjuvant treatment[1, 9]. Unfavorable growth parameters in the tumor front (i.e. IG, PG and BI) are believed to be a relative indication for adjuvant treatment[1]. Table 3 shows the criteria for adjuvant treatment set against the local recurrence risk, according to the DHNS[19].

Table 3. DHNS criteria for local adjuvant treatment

Criterion	Risk	Management
Positive margin <1mm	→ High risk	→ (chemo)PORT or re-resection
Close margins 1-5 mm T3 or T4 IG PN	→ Intermediate risk	→ Consider PORT
No "unfavorable" pathological parameters	→ Low risk	→ No adjuvant treatment

The prevalence of these histopathological parameters varies in literature from 10 to 61 %[20-22]. The considerable IOV among pathologists found in this study may explain this variation. Pathology observations used for treatment planning should not only be biologically meaningful but also reproducible between pathologists to have a substantial validity[10]. IG, PG and BI are known to be associated with loco-regional recurrence, prognosis and consequently are clinically relevant[20, 23, 24]. The moderate to slight interobserver agreement of these parameters in this study shows that the reproducibility, even among dedicated head and neck pathologists is not optimal. This is important as it has clinical implications. The same patient would in one center be scheduled for adjuvant treatment (i.e. close resection margins combined with ≥2 growth parameters) whereas in another center he/she would only be followed up. Figure 2 d shows that in the two centers with the most diverse observations (center C and F, 33% concordance) even 67% of the patients might have had a different treatment plan according to the DHNS guidelines. This variation in treatment planning

depending on the hospital and its pathologist, obviously is highly undesirable. There can be various reasons for the poor IOV in this study: First, the unclear definition and consequently subjective interpretation of the different histological parameters leaves room for a wide variability[14, 17]. Since no consensus meetings where performed in advance, the participating pathologists may have used subjective interpretations of the definitions of the various pathological parameters BI, PG and IG. After discussion of the results we used this lack of consensus to come to more specific definitions on these pathological growth features. After a consensus meeting the following definitions of growth parameters where formulated: BI was defined as infiltration of tumor cells through the cortical bone. Solely erosion of the cortical bone was not classified as bone invasion[25]. IG was defined based on the presence of non-cohesive tumor cells that form an ill-defined edge with formation of strands with or without isolated tumor islands [26]. PG was defined as the presence of malignant cells within the perineurium at the tumor front [27] Secondly, variations in screen quality, used magnifications or other screen settings between the individual pathologists may have been different, since no instructions were provided how to judge the digital sections. As such, this study should not be seen as a validation study for assessing head and neck pathology cases by digital pathology. Thereby others state that not the digital slides but the pathologist's competence is the crucial factor[28]. digital slides are proven non-inferior compared to conventional microscopy[28,29]. Although unlikely, the experience in judging digital slides per se, may play a role in poor IOV, since this is not routine pathological practice yet. The application of digital H&E sections is however beneficial: digital slides don't take up any physical space and peer consultations are faster and more efficient because of the limitless availability of the H&E sections worldwide[28]. This could reduce diagnostic delay and potentially provide better outcome in the future. Others already reported that the diagnostic reliability of a fully digital slide-based system is comparable with the conventional optical microscope and is applicable in routine pathological practice in a wide variety of organ systems and specimen types[28, 29]. In other diagnostic fields of medicine, i.e. radiology, IOV is an important factor in deciding whether a diagnostic tool is reliable enough to use in patient treatment[30]. For instance, in a study concerning the detection of distant metastasis in head and neck cancer patients, the use of whole body FDG-PET with an almost perfect agreement (kappa 0.83-0.94) will be naturally preferred above an ordinary chest CT with only a moderate to substantial agreement (kappa 0.41-0.51)[31]. However, despite optimal implementation and definition making, an unsatisfactory IOV might still persist as described in radiology[30]. In the prediction of tumor behavior based on pathology findings, other techniques, such as gene expression profiling or the determination of chromosomal instability in resection margins, with a possibly better IOV are not yet broadly introduced in routine clinical practice[32, 33]. Therefore, validation and pinpointing definitions of pathological growth parameters and training in interpretation of the current diagnostic tool i.e. digital assessment of H&E sections is mandatory and may lead to a better IOV.

In conclusion, histopathological parameters play a key role in further treatment planning following primary surgery of OSCC. With at most a moderate agreement in case of digital examination of H&E slides, current reproducibility is not reliable enough and findings cannot be used to guide adjuvant treatment planning in daily clinical practice. Improvement of IOV is mandatory. If clinicians want to believe that histopathological parameters are of importance in treatment planning, clear and transparent definitions in quality of screens and screen settings as well as establishing clear definitions for the different histological parameters by regular consensus meetings may contribute to a better reproducibility[15, 34]. As such, this study could serve as a baseline, to evaluate the effect of future training and consensus meetings.

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5

CHAPTER FIVE

Resection of early oral squamous cell carcinoma with positive or close margins: Relevance of adjuvant treatment in relation to local recurrence Margins of 3 mm as safe as 5 mm

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ABSTRACT

Objectives The treatment strategy of early stage oral squamous cell carcinoma's (OSCC) resected with close or involved margins is a returning point of discussion. In this study we reviewed the consequences of re-resection (RR), postoperative radiotherapy (PORT) or watchful waiting (WW).
Patients and methods Two-hundred patients with a primary resected Stage 1–2 OSCC of the tongue, floor of the mouth and cheek were included and retrospectively analyzed. Local recurrence ratio was related to margin status, unfavorable histological parameters (spidery infiltrative, perineural and vascular-invasive growth) and postoperative treatment modality. 3-year overall survival (OS) and disease-specific survival (DSS) was calculated in relation to margin status.
Results Twenty-two of 200 (11%) patients had pathological positive margins (PM), 126 (63%) close margins (CM), and 52 (26%) free margins (FM). OS and DSS were not significantly different between these groups. Nine of 200 (4.5%) patients developed local recurrent disease. Two (9.1%) had a PM, five (4.0%) a CM and two (3.8%) a FM. Of the nine recurrences, five patients had undergone PORT, one a RR, and three follow-up. Watchful waiting for CM $\geqslant$3 mm with $\leqslant$2 unfavorable histological parameters showed, besides margin status no significant differences with the FM group.
Conclusion With this treatment strategy, the local recurrence rate was 4.5%. No evidence was found for local adjuvant treatment in case of close margins $\geqslant$3 mm with $\leqslant$2 unfavorable histological parameters. Current data do not support the use of one treatment modality above any other.

Introduction

For Stage I-II oral squamous cell carcinoma (OSCC) the preferred choice of treatment is complete surgical removal of the tumor. To achieve the best results in loco-regional control and long-term disease-free survival, several authors believe that free resection margins of at least 5 mm are essential[1-4], while others disagree[5-7]. Complete removal should ideally be achieved at the first surgical procedure[2]. However, in 5–13% of resected early OSCCs, microscopic tumor is present in the resection margin, known as a "positive" margin[2]. A positive margin carries a high risk of recurrence and is an indication for adjuvant treatment such as irradiation or re-resection[2,8,9]. Another 15–42% of resected OSCCs have a margin between 0 and 5 mm, known as a "close" margin[8,10]. In close margins, histological parameters of the tumor front such as spidery infiltrative growth, perineural and vascular invasive growth may influence the certainty whether or not microscopic tumor is still present. Opinions vary about the impact of these parameters on local control and disease-free survival and whether or not to implement adjuvant treatment[7,8,10-13]. If a margin is close, evidence in favor of either adjuvant treatment or a policy of "watchful waiting", is lacking. In this retrospective study, we review the treatment strategy of Stage I-II OSCC with positive or close margins at our department. In case of close margins, we compared surgical re-resection with adjuvant radiotherapy and a watchful waiting policy. These results were compared with those of resected early stage OSCC with margins >5 mm, designated as "free" margins.

Patients and methods

Between 2004 and 2010, 226 patients had primary surgery for a Stage I-II OSCC of the tongue, the floor of the mouth or the cheek mucosa. Patient charts were analyzed retrospectively. Twenty-six patients were excluded: 21 because they had been treated for a previous head and neck malignancy and five because they underwent both re-resection and radiotherapy for the same tumor. A total of 200 patients were included in this study.

Before treatment, a multidisciplinary team, consisting of a head and neck surgeon, pathologist, radiologist and radiation oncologist, discussed every patient. The trans-oral excision included a macroscopic safety margin of 10 mm. In 125 patients, a selective neck dissection (levels I–III) was performed. All operations were performed by one of four experienced head and neck surgeons. A dedicated head and neck pathologist assessed all resected specimen. The margin status, tumor diameter, tumor thickness, and the histological parameters of the tumor front, i.e. spidery infiltrative growth, perineural and vascular invasive growth, were determined. The latter three characteristics were defined as "unfavorable histological parameters". If margins were positive or close the location of the closest margin – deep or mucosal – was determined.

Based on resection margin status, we created three groups: a pathologically positive margin (PM), close margin (CM) and free margin (FM) group (Table 1).

Table 1. Definition of patient groups based on pathological margin status.

Group	Definition	n (%)
PM	Positive margins, microscopically tumor cells present in the resection border	22 (11)
CM	Close resection margins >0–5 mm	126 (63)
FM	Free resection margins >5 mm	52 (26)

After resection, the choice of whether to implement adjuvant treatment was based on the pathological findings and tumor characteristics of the resection specimen. There were three options for further patient management:

Re-resection (RR) was defined as a repeat resection at the primary tumor site during a second intervention. RR was chosen in patients with a PM or CM situated mainly at the mucosal resection border. Margins had to be locatable by a pathologist and surgically resectable. The acceptable number of unfavorable histological parameters was generally $\leqslant 2$.

Postoperative Radiotherapy (PORT) was defined as 'local irradiation of the primary resection site'. PORT was the treatment of choice in patients with a PM or CM situated mainly at the deep resection margin and $\geqslant 2$ unfavorable histological parameters. Regional radiotherapy of the neck in case of lymph node metastasis was labelled differently and excluded from this analysis.

Watchful Waiting (WW) was defined as a close follow up (every 1–2 months for three years postoperatively) without adjuvant treatment. This policy was generally chosen in cases of a CM $\geqslant 3$ mm with $\leqslant 2$ unfavorable histological parameters.

Patients in the PM group received adjuvant treatment. This comprised either radiotherapy (66 Gy) or re-resection at the primary tumor site. One patient with PM received no adjuvant treatment for unknown reasons. Patients in the CM group were either allocated to RR, PORT (56 Gy) or WW. Patients in the FM group received no adjuvant therapy.

Results were analyzed according to the incidence of local recurrence during follow-up, classified as the recurrence of OSCC at, or adjacent to, the primary site within three years of the incidence date of the first tumor. The distribution of recurrences over the three groups (i.e. PM, CM and FM) and the various treatment modalities (i.e. RR, PORT and WW) were determined. For the groups PM, CM and FM survival curves were calculated. Three-year overall survival (OS), was calculated from the date of first histological confirmation of OSCC to the date of death from any cause. The three-year disease-specific survival (DSS) was the secondary outcome. For DSS-rates censoring occurred at the date of death from causes other than OSCC or at the end of the follow-up period, whichever came first.

Patients and tumor characteristics in relation to the margin status and the type of adjuvant treatment were analyzed and compared. Patients in the WW group (with CM) were compared to patients in the FM group. Three-year OS- and DSS-rates were determined for these two groups as well. Characteristics of the patients are reported as frequency (percentage) for categorical variables. Continuous variables are presented as mean (SD) when normally distributed or median (range) when not. Gaussian distribution was confirmed by visual analysis of the histograms, Q–Q plots and the Shapiro–Wilk test. One-way ANOVA was used for hypotheses testing of normally distributed continuous data and Mann–Whitney U test and Kruskal–Wallis test for continuous data that were not normally distributed. For categorical data P-values were calculated with the use of Fisher's exact tests. Using life table techniques, DSS-rates and OS-rates were calculated, illustrated by Kaplan–Meier plots. Covariates were compared with the log-rank test. All test statistics were two tailed, and the significance level was set at $p < 0.05$. Survival analyses were performed with Stata Statistical Software (Release 12. College Station, TX: StataCorp LP) All other analyses were performed with the use of Statistical Package for the Social Sciences (SPSS for windows, release 20.0.0 2011, SPSS Inc.).

Results

In the total cohort of 200 patients, 22(11%) had a PM, 126(63%) a CM, and 52(26%) a FM. The three patient groups did not differ regarding tumor site, patients' habits, gender or age. Also, there were no differences in the unfavorable histological parameters. A significant difference was found with relation to tumor diameter and thickness ($p = 0.005$ and $p = 0.002$ respectively): in the CM group, tumors were bigger than those in the PM and FM group. Table 2 shows all relevant data of the 200 patients included in the study. Nine out of 200 (4.5%) patients developed recurrent disease at the primary site. Distribution over the different sub-sites is shown in Table 4. Recurrences were located at the tongue in 6/105 (5.7%), the floor of mouth in 2/75(2.7%) and inside the cheek in 1/22 (4.5%). In the PM, CM and FM groups, respectively two (9.1%), five (4.0%) and two (3.8%) patients had local recurrent disease. Of the two patients with local recurrence in the PM group, one had undergone a RR and one PORT.

Of the five local recurrences in the CM group, four had received PORT and one was selected for WW. Of all nine recurrences, five patients had undergone PORT, one a RR, and three developed during WW (Tables 3 and 4, Fig. 1).

Table 2. Patient characteristics.

Variables (n = 200)	PM n = 22	CM n = 126	FM n = 52	P-value
Gender – no. (%)				a
Male	13 (59)	72 (57)	28(54)	0.91
Female	9 (41)	54 (43)	24 (46)	
Age – yr				b
Mean	58.9	63.3	61.1	0.21
SD	12.8	12.6	11.4	
Range	31–83	23–90	36–86	
Smoker – no. (%)				a
Yes	9 (41)	67 (53)	26 (50)	0.57
No	13 (59)	59 (47)	26 (50)	
Alcohol – no. (%)				a
Yes	12 (55)	73 (58)	30 (58)	0.95
No	10 (45)	53 (42)	22 (42)	
Site – no. (%)				a
Tongue (n = 105)	11 (50)	67 (53)	27 (52)	0.96
Floor of mouth (n = 73)	9 (41)	46 (37)	18 (35)	
Cheek (n = 22)	2 (9)	13 (10)	7 (13)	
Tumor diameter (mm)				c
Median	11.0	17.5	12.0	0.005
Range	2–36	1–40	1–40	
Tumor thickness (mm)				c
Median	3.0	5.8	4.0	0.002
Range	1–16	1–30	1–20	
Growth pattern – no. (%)				a
Spidery	16(73)	81 (64)	28(54)	0.26
Peri-neural	7 (32)	36 (29)	7 (13)	0.07
Angio-invasive	3 (14)	12 (10)	2 (4)	0.30

a P values were determined by Fisher's exact test.

b P values were determined by one-way ANOVA.

c P values were determined by Kruskal–Wallis test.

Table 3. Adjuvant therapy in relation to patient groups and recurrences.

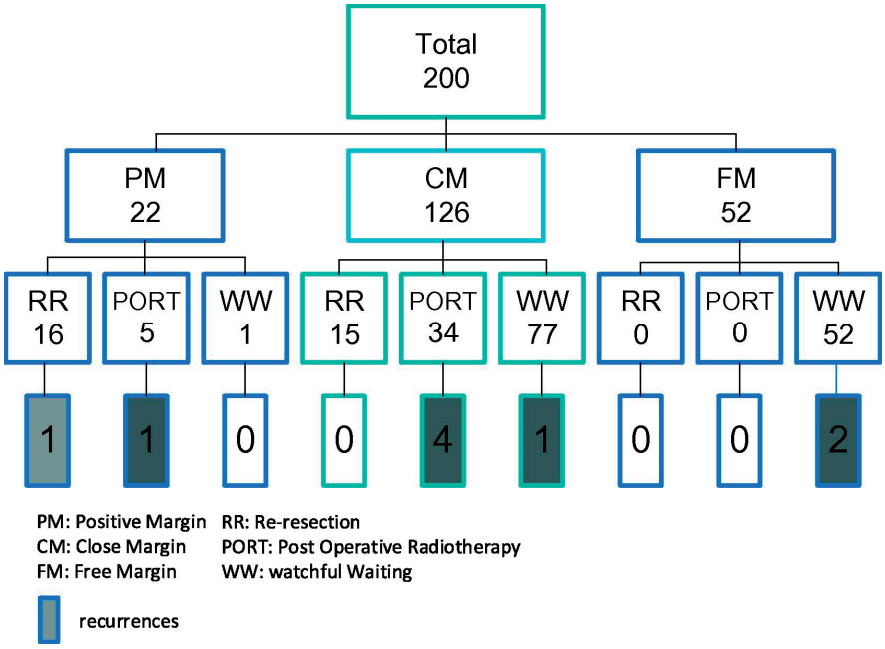
Variables (n = 200)	PM n = 22	CM n = 126	FM n = 52	Total recurrence no. (%)
Recurrence	*2*	*5*	2	9
RR n = 31	**16** *1*	**15** *0*	**0** *0*	1 (3)
PORT n = 39	**5** *1*	**34** *4*	**0** *0*	5 (13)
WW n = 130	**1** *0*	**77** *1*	**52** *2*	3 (2)

Bold: *The amount of patients in relation to margin status and treatment modality. Italic: The amount of patients with local recurrence in relation to margin status and treatment modality.*

Table 4. Distribution of recurrence in relation to margin status.

Variables (n = 200)	PM n = 22	CM n = 126	FM n = 52
Recurrence – no. (%)	2 (9.1)	5 (4.0)	2 (3.8)
Site of recurrence – no. (%)			
Tongue	0	4 (3.2)	2 (3.8)
Floor of mouth	1 (4.5)	1 (0.8)	0
Cheek	1 (4.5)	0	0

Figure 1. Flowchart of patient groups, type of treatment and recurrence rate.



Comparison of patients in the WW group (n = 77) with those of the FM group (n = 52) showed, as expected due to selection, a significant difference in margin status ($p < 0.001$) with a median resection margin of 3.0 mm (range 1–5) in the CM group and 6.0 mm (range 5.1–10) in the FM group. However, no significant difference in development of local recurrence was encountered, being 1/77(1.3%) in the WW and 2/52 (3.8%) in de FM group. Also unfavorable histological parameters, thickness and diameter were not significantly different between these groups (Table 5).

Table 5. Recurrence and pathological characteristics of group WW (with CM) and FM.

Variable (n = 129)	WW (with CM) n = 77	FM n = 52	P value
Local recurrence			a
Yes	1 (1)	2 (4)	0.57
No	76 (99)	50 (96)	
Spidery growth – no. (%)			a
Yes	44 (57)	28 (44)	0.72
No	33 (43)	24 (56)	
Perineural growth – no. (%)			a
Yes	13 (17)	7 (14)	0.81
No	64 (83)	45 (87)	
Angio invasive growth – no. (%)			a
Yes	4 (5)	2 (4)	1.0
No	73 (95)	50 (96)	
Tumor diameter (mm)			b
Median	13.0	12.0	0.23
Range	1–40	1–40	
Tumor thickness (mm)			b
Median	4.0	4.0	0.33
Range	1–30	1–20	

a P values were determined by Fisher's exact test.
b P values were determined by Mann–Whitney U test.

The three-year OS was 91% (95% CI 68–98%) in group PM, 87% (95% CI 80–92%) in group CM and 87% (95% CI 74–93%) in group FM (p = 0.86). The three-year DSS was 95% (95% CI 72–99%) in group PM, 91% (95% CI 84–95%) in group CM, and 90% (95% CI 78–96%) in group FM (p = 0.76). In group WW with CM the three-year OS was 91% (95% CI 82–96% p = 0.41) and the three-year DSS was 93% (95% CI 85–97% p = 0.49).

Fig. 2 shows the Kaplan Meier survival curves of the mentioned groups.

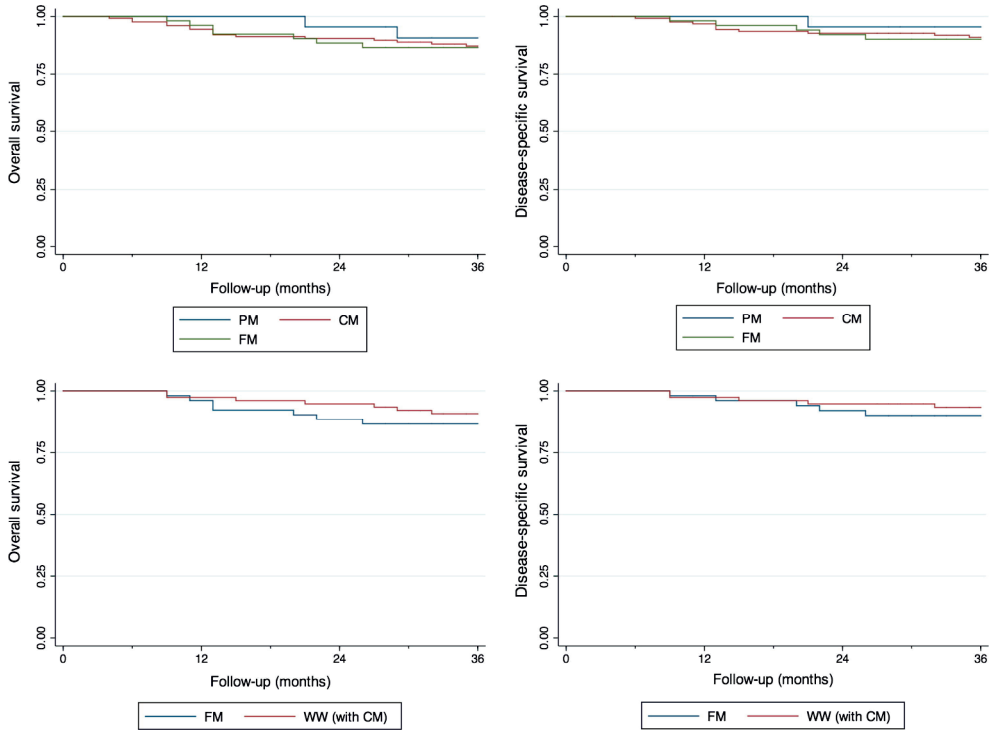


Figure 2. Kaplan Meier survival curves of group PM, CM, FM and group WW with CM.

Discussion

Our current strategy in treating early stage OSCC is effective, as it resulted in only 4.5% local recurrences, which concurs with the lower limit of percentages mentioned in the literature ranging from 4% to 22%[7,14-16]. Most recurrences are located at the tongue (5.7%) followed by the cheek (4.5%) and floor of the mouth (2.7%).

These results are similar to those reported by others[12,14,17]. Sixty-three percent of the OSCC's was resected with close margins. In literature this percentage ranges between 15% and 42% [8,10]. An explanation could be our group distribution, which was based on margin status. As our margins between 0 and 5 mm are classified as close and others consider margins ⩽1 mm or more as positive[4], this may have resulted in a shift of patients form the positive margin to the close margin group.

Another explanation is our pathological analysis. Margins were measured in millimeters with 1 decimal accuracy and were not rounded, which probably led to a bigger proportion of OSCC's resected with close margins.

The management of positive or close margins is a recurring point of discussion among clinicians. There is no consensus about which adjuvant treatment modality to use in case of a positive margin[1-4,9]. As positive margins have an adverse effect on local control, many authors state adjuvant treatment is justified[1-4,9,12,18]. Our study underscores this statement. Even despite adjuvant treatment, 9% of the resected OSCC with a PM recurred locally compared with 4.0% in the CM group and 3.8% in the FM group.

In case of close margins, no consensus about the necessity of adjuvant treatment exists. Some authors state close margins between 0 and 5 mm are strongly related to local control[3,4,12,18], while others refute this[5,7,19]. No prospective randomized clinical trials are available to answer this question. Most studies have a retrospective design [8,11,12,20,21] and because of the low numbers of local recurrences, significant conclusions are often impossible to draw[11,12]. We found a similar level of recurrence, OS and DSS in the CM and FM groups, which suggests that free margin status is irrelevant. However, the CM group is an inhomogeneous group: 34/126 (27%) patients received PORT, 15/126 (12%), underwent RR and 77/126 (61%) received no adjuvant therapy at all (Table 3). Therefore, only a comparison between the WW group with CM and FM groups is justified (Table 5), showing a local recurrence of 1.3% and 3.8% respectively (not significant). As, apart from resection margins averaging 3 mm in the WW group and 6 mm in the FM group, no significant differences in pathological parameters, OS and DSS between these groups were seen, it can be concluded that where local recurrence risk is concerned, at least a free margin of 3 mm is just as safe as one of 6 mm. Indeed, it could be argued that the whole concept of using a free margin status is irrelevant in early oral cancer: once resection margins are clear, recurrence risk is extremely low, as has previously been demonstrated[5,7]. A substantial proportion of the CM group may have undergone PORT or RR without evident necessity or benefit while causing extra morbidity and expenses[22,23]. In comparison to our 1985–1994 cohort of Stage I-II oral cancers, in which no adjuvant treatment for CM was given, this treatment strategy did not alter the risk of local recurrence[7]. Therefore the "close margin concept" introduced a decade ago seems irrelevant in making decisions on adjuvant treatment for Stage I-II oral cancers[10-11].

Many authors suggest that histological parameters such as depth of tumor infiltration[14,18,24-26], perineural ingrowth vasoinvasive growth and spidery growth are also related to poor local control[2,10,12,19,20,27], and hence indicate adjuvant treatment. Our study could not endorse that statement. Also, in this study, a multivariate analysis of pathological parameters was not possible due to the small recurrence numbers.

In case of PM or CM, local adjuvant treatment is performed in a considerably proportion of the cases. Some authors suggest RR[2,3,8,14]. Others suggest postoperative radiotherapy[5,9,19,28], while accepting its adverse side-effects[22,23]. Most recurrences occurred in the PORT group with 13% compared to 3% in the RR group. This suggests RR to be the type of treatment to choose in case of positive or close margins <3 mm, locatable by a pathologist and reachable for resection. To check whether our non-significant results were due to a lack of statistical power, a post hoc power analysis was conducted using Stata Statistical Software (Release 12. College Station, TX: StataCorp LP), with power (1-β) set at 0.80 and α at .05, two-tailed. The post hoc power analysis (RR vs PORT) revealed that with a recurrence rate of 3% in the re-resection group and 13% in the PORT group, at least 145 patients in both groups would be needed to reach significance. This implies that at least 5 times as many patients should be included in each treatment group. In total, over a thousand early OSCC's should be included to reach significance. Thus, due to the low number of recurrences and the consequential impossibility to reach significance, the preference for a local RR, PORT or WW could not be estimated on this material. Another important factor is the selection bias. OSSC's with deep margin involvement not reachable for a re-resection and $\geqslant$2 unfavorable histological parameters were treated with PORT. The more unfavorable OSCC's are in this group, which probably explains the higher amount of recurrences.

In conclusion, this study demonstrates that, what local recurrence is concerned, there is no evidence for local adjuvant treatment in case of resection margins $\geqslant$3 mm with $\leqslant$2 unfavorable histological parameters. A meta-analysis of available literature could contribute to answer the question in which cases what type of local adjuvant treatment is relevant for incompletely removed early oral cancers.

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6

CHAPTER SIX

Watchful waiting of the neck in early stage oral cancer is unfavorable for patients with occult nodal disease

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ABSTRACT

For cT1/2N0 oral squamous cell carcinoma (OSCC), treatment of the neck is a matter of debate. Two treatment strategies were evaluated in this study: selective neck dissection (SND) and watchful waiting (WW). One hundred and twenty-three SND patients and 70 WW patients with cT1/T2N0M0 OSCC of the tongue, floor of mouth, or buccal mucosa were analyzed retrospectively. Extracapsular spread (ECS), 3-year overall survival (OS), and disease-specific survival (DSS) were determined. Twenty-nine percent of SND patients and 13% of WW patients had occult nodal disease. WW-N+ patients showed thicker tumors as compared to WW-N0 patients (5 mm vs. 2 mm, $P = 0.02$). WW-N+ patients showed significantly more ECS as compared to SND-N+ patients (56% vs. 14%, $P = 0.016$) and had a significantly worse 3-year DSS than SND-N+ patients (56% vs. 82%, $P = 0.02$). For T1 OSCCs, a watchful waiting policy is acceptable if tumor thickness proves to be <4 mm. Otherwise, an additional treatment of the neck is advised, since WW-N+ patients show more ECS, with a worse DSS than SND-N+ patients.

Introduction

For most patients with early stage (T1/T2N0) oral squamous cell carcinoma (OSCC), the preferred treatment is surgical excision of the primary tumor. The management of the clinically negative neck (cN0) remains a matter of debate[1-6].The intervention and related side effects of a selective neck dissection (SND) or elective radiation therapy must be weighed against the benefits of possibly better regional control. About 20–40% of early stage OSCC patients have occult nodal disease in the neck[3,5,7,8]. Despite imaging, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasonography (US), and even fine needle aspiration cytology (FNAC), a substantial proportion of these metastases remain undetected[4,9,10].

Gene or protein expression profiling of the primary tumor, which may have additional value for the identification of tumors with a high propensity for early metastatic spread,7,11 is not yet applied routinely.7 Also the sentinel node biopsy for OSCC has still not gained wide acceptance. The decision whether or not to treat the cN0 neck is therefore often based on a combination of clinicopathological tumor characteristics, imaging, and FNAC[3,4,8,12]. Consequently, patients with a true pN0 neck may receive an unnecessary SND with the risk of perioperative and postoperative complications[13,14]. Alternatively, proper treatment may be withheld from patients with a true pN+ neck, and these patients may be confronted with lymph node metastases during follow-up, sometimes even with extracapsular spread (ECS). Some studies report that a 'watchful waiting' (WW) policy can be accepted for small oral cancers[15,16].

The aim of this retrospective study was to evaluate the current treatment strategy of the cN0 neck in stage I–II OSCC at the authors' institution. This strategy consists of a SND for cT1–T2N0M0 OSCCs and watchful waiting in the case of cT1N0M0 OSCCs with a diameter of <15 mm and thickness of <5 mm. The distribution of occult metastases, the incidence of ECS, and survival rates were analyzed.

Patients and methods

Patients

A retrospective chart review was conducted of 226 consecutive patients with pT1–2 cN0 OSCC of the tongue, floor of the mouth, or buccal mucosa (International Classification of Diseases for Oncology 3rd edition (ICD-O-3) locations C02.0–C02.3, C04, and C06.0), who were treated with a primary surgical resection between 2004 and 2010. Thirty-three patients were excluded: 21 because of a previous head and neck malignancy, two because a sentinel node biopsy was performed, three because they had received primary radiotherapy of the neck, and seven because a SND was indicated (see below) but not done due to co-morbidity. Staging was performed in accordance with the 2002 Union for International Cancer Control (UICC) criteria. Pertinent data are listed in Table 1.

Table 1. Clinicopathological characteristics of cN0 patients according to the type of treatment.

Characteristics	SND (n = 123)	WW (n = 70)	P-value
Sex, n (%)			0.14a
Male	75 (61)	35 (50)	
Female	48 (39)	35(50)	
Age (years)			0.25b
Mean (SD)	62 (11)	64 (15)	
Range	35–86	23–90	
ECOG score, n (%)			0.10c
0	87 (78)	39 (65)	
1	18 (16)	12 (20)	
≥2	6 (5)	9 (15)	
Smoking, n (%)			0.06a
Yes	68 (55)	29 (41)	
No	55 (45)	41 (59)	
Alcohol, n (%)			0.94a
Yes	71 (58)	40 (57)	
No	52 (42)	30 (43)	
Primary tumor site, n (%)			0.28a
Tongue	67 (55)	32 (46)	
Floor of mouth	42 (34)	32 (46)	
Cheek	14 (11)	6 (9)	
Tumor diameter (mm)			<0.001d
Median	20.0	7.5	
IQR	13.5–26.5	3.5–11.5	
Tumor thickness (mm)			<0.001d
Median	7.0	2.0	
IQR	3.0–11.0	1.0–3.0	
Growth pattern, n (%)			
Infiltrative	84 (68)	36 (51)	0.02a
Perineural	42 (34)	5 (7)	<0.001c
Vascular invasive	14 (11)	0 (0)	0.002c

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SD, standard deviation; SND, selective neck dissection; WW, watchful waiting.

a Pearson's χ2 test.
b Unpaired t-test.
c Fisher's exact test.
d Mann–Whitney U-test.

Methods

CT or MRI was performed for OSCCs staged as cT2 and cT1 with a clinically estimated infiltration depth of ≥5 mm. US of the neck was performed with FNAC when a node showed a short transverse diameter >5 mm, an abnormal shape, or a deviant architecture. A SND was performed in all patients with a suspicion of nodal disease on US, not confirmed by FNAC, or an estimated infiltration depth of more than 5 mm.
Patients were assigned to a WW policy for cT1 tumors with both a clinical diameter <15 mm and an estimated infiltration depth <5 mm, and if no nodal disease was suspected on imaging or FNAC. The surgical intervention consisted of wide transoral excision of the tumor (10-mm macroscopic margins), with or without an intentional SND level I–III, performed by one of four surgeons specialized in head and neck surgical oncology.

SND patients underwent surgical resection of the primary tumor combined with an intentional SND level I–III, not necessarily en bloc. During the operation, frozen sections were made for the histopathological examination of suspicious lymph nodes. In the case of metastasis, a modified radical neck dissection was performed in the same procedure.

WW patients underwent surgical resection of the primary tumor without treatment of the neck. US examination was intended every 3–4 months in the first postoperative year, or in the case of palpable nodes. The development of regional metastases and the distribution over different subgroups was analyzed. All patients were followed-up for at least 3 years.

Within these two groups, two subgroups were identified: (1) SND-N+ patients, who were patients with occult nodal metastasis in the SND group, i.e. patients in the SND group with either a pathological positive neck (pN+) or with a pathological negative neck (pN0) who developed regional metastasis without local recurrence during follow-up, and (2) WW-N+ patients, who were patients with occult nodal metastasis in the WW group, i.e. patients in the WW group who developed regional metastasis without local recurrence during follow-up.

Figure 1 shows the total cohort and the different subgroups.

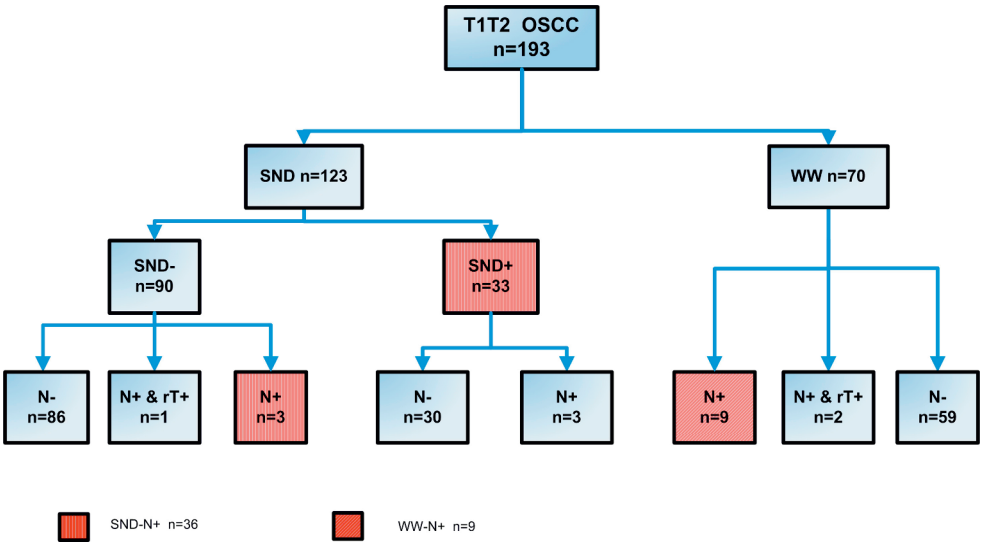

Fig. 1. Distribution of occult metastasis (SND, selective neck dissection; WW, watchful waiting; SND−, no pathological positive lymph nodes in SND specimen; SND+, pathological positive lymph nodes in SND specimen; N−, no regional metastasis during follow-up; N+, regional metastasis during follow-up; N+ & rT+, regional metastasis and local recurrence; SND-N+, patients with occult nodal metastasis in the SND group; WW-N+, patients with occult metastasis in the WW group).

Histological analysis

A dedicated head and neck pathologist (SMW) assessed the surgical resection specimens of the primary tumor and lymph nodes of the neck dissection. Margin status, tumor diameter, tumor thickness, and the presence of perineural growth, infiltrative growth, and vascular invasive growth were determined. The presence of metastases and ECS was determined for every neck dissection specimen. Nodes were examined by cutting every node in half, without stepped serial sectioning or immunohistochemistry. The location was determined using the level system described by Robbins et al.17

Statistical analysis

Patient characteristics are reported as the frequency and percentage for categorical variables; continuous variables are reported as the mean and standard deviation when normally distributed, or as the median and interquartile range (IQR) if not. The unpaired t-test was used for hypothesis testing of normally distributed continuous variables, and the Mann–Whitney U-test for continuous data that were not normally distributed. The calculation of P-values for categorical data was done using Pearson's $\chi 2$ test or Fisher's exact test, as appropriate.

Using life-table techniques, 3-year disease-specific survival (DSS) and overall survival (OS) rates were calculated and illustrated as Kaplan–Meier plots. OS was calculated from the date of diagnosis to the date of death from any cause. For DSS, censoring occurred at the date of death from causes other than OSCC or at the end of follow-up, whichever came first. Covariates were compared with the log-rank test. All test statistics were two-tailed, and the significance level was set at $P < 0.05$. Analyses were performed using IBM SPSS for Mac version 22.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Of the 193 patients included in this study, 123 underwent a SND and 70 were assigned to a WW policy (see Table 1 for clinicopathological characteristics of the two groups). Age, sex, Eastern Cooperative Oncology Group (ECOG) score, primary tumor site, and smoking and drinking habits were comparable in the two groups. The median tumor diameter and thickness were about three times greater in SND patients than in WW patients (both $P < 0.001$). Primary tumors of SND patients showed significantly more infiltrative ($P = 0.02$), perineural ($P < 0.001$), and vascular invasive ($P = 0.002$) growth.

Treatment groups

In the SND group, 36 out of 123 patients (29%) had occult nodal disease. Six of these patients (5%) received a modified radical neck dissection in the same surgical procedure because frozen sections of a suspected lymph node confirmed metastatic disease. Thirty-three patients (27%) were pN+, with ECS in four. Another three of the 90 pN0 patients developed nodal metastases during follow-up, all three out of field: two at level IV and one high parapharyngeal, one patient with a node with ECS and two in whom the presence of ECS could not be determined because a neck dissection was not performed. As a result, at least five and possibly seven of 123 patients (4–6%) in the SND group had nodal metastasis with ECS. One SND patient had regional metastases as well as a local recurrence. Because of possible reseeding, this patient was not classified as having occult metastasis (Fig. 1).

In the WW group, regional metastasis occurred on average after 9.89 months (range 4–22 months) in nine out of 70 (13%) patients. ECS was present in five patients and absent in two; the presence of ECS could not be determined in two cases, because a neck dissection was not performed. As a result, at least five and possibly seven out of 70 patients (7–10%) with occult metastasis in the WW group showed ECS. All metastases were located on the ipsilateral side. Two (3%) WW patients had regional metastases as well as a local recurrence. Because of possible reseeding, these two patients were not classified as occult metastasis (Fig. 1). Fifty-nine (84%) WW patients had no regional disease (Fig. 1).

In the WW-N+ group, median tumor thickness was significantly higher as compared to WW patients without occult metastasis (WW-N0) (5 mm vs. 2 mm, P = 0.02). No significant differences were found for tumor site, diameter, or growth pattern (Table 2).

Table 2. Tumor characteristics of WW-N0 and WW-N+ patients.

Characteristics	WW-N0 (n = 59)	WW-N+ (n = 9)	P-value
Primary tumor site, n (%)			0.17a
Tongue	24 (41)	7 (78)	
Floor of mouth	29 (49)	2 (22)	
Cheek	6 (10)	0 (0)	
Tumor diameter (mm)			0.13b
Median	7.0	12.0	
IQR	3.5–10.5	7.5–16.5	
Tumor thickness (mm)			0.02b
Median	2.0	5.0	
IQR	1.0–3.0	3.5–6.5	
Growth pattern, n (%)			
Infiltrative	29 (49)	6 (67)	0.48a
Perineural	4 (7)	1 (11)	0.52a
Vascular invasive	0 (0)	0 (0)	–

IQR, interquartile range; WW, watchful waiting; WW-N0, patients without occult nodal metastasis in group WW; WW-N+, patients with occult nodal metastasis in group WW.

a Fisher's exact test.
b Mann–Whitney U-test.

In the total cohort of 193 cT1–2N0 patients, 45 (23%) had occult nodal metastasis: 33 cases were identified from the neck dissection specimen (SND group) and 12 emerged during follow-up (nine in WW patients and three in SND patients). There was no difference in the number of lymph nodes with ECS in the SND group (4–6%) and the WW group (7–10%). However, of all patients who had positive lymph nodes, a significantly larger number of positive lymph nodes with ECS was found in WW-N+ patients as compared to SND-N+ patients (56% vs. 14%, P = 0.016). Three patients (2%) developed both a local recurrence and possibly new nodal metastases, i.e., reseeding. In total, 145 patients (75%) remained free of regional metastasis (Fig. 1).

Survival

The median follow-up was 58 months (IQR 37–79 months). The 3-year OS was 90% (95% confidence interval (CI) 85–95%) in SND patients and 86% (95% CI 78–94%) in WW patients (P = 0.54). The 3-year DSS was also similar in the two groups, being 93% (95% CI 89–98%) in SND patients and 88% (95% CI 81–95%) in WW patients (P = 0.20). The estimated 3-year OS was 75% (95% CI 61–89%) in SND-N+ patients and 56% (95% CI 23–89%) in WW-N+ patients (P = 0.19). SND-N+ patients had a significantly better 3-year DSS than WW-N+ patients, being 82% (95% CI 69–95%) versus 56% (95% CI 23–89%) (P = 0.02). Figure 2 shows the Kaplan–Meier survival curves of the groups mentioned.

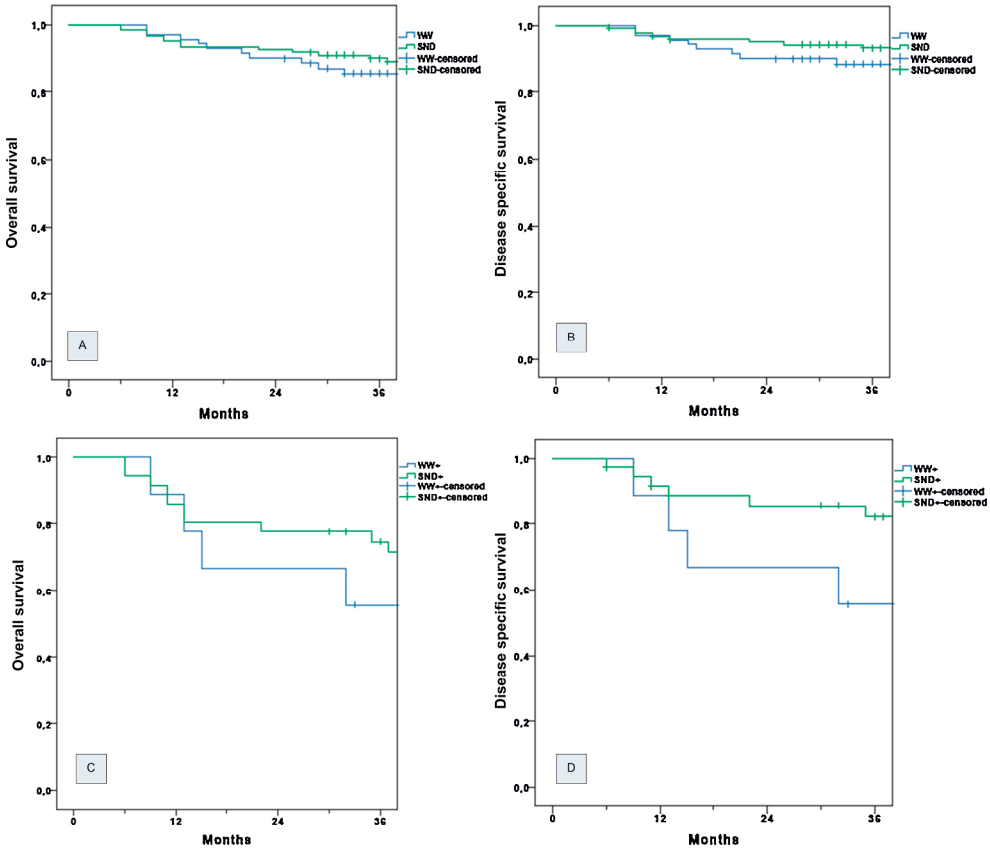

Fig. 2. Survival curves of SND, WW, SND-N+, and WW-N+ groups. (A) Overall survival group SND and WW (P = 0.54). (B) Disease-specific survival group SND and WW (P = 0.20). (C) Overall survival group SND-N+ and WW-N+ (P = 0.19). (D) Disease-specific survival group SND-N+ and WW-N+ (P = 0.02). (SND, selective neck dissection; WW, watchful waiting; SND-N+, patients with occult nodal metastasis in the SND group; WW-N+, patients with occult metastasis in the WW group.).

The 3-year OS and DSS of the six SND-N+ patients who received a modified radical neck dissection during the same procedure were not significantly different from those of the SND-N+ patients who received only a SND (P = 0.83 and P = 0.30, respectively).

Discussion

In this cohort of 193 early stage OSCC patients, 23% had occult nodal disease, which is in agreement with the lower bounds of percentages reported from other studies[2,3,6,7]. Explanations for this may include the application of US-guided FNAC and the predominance of small cancers in the material studied, as tumors of a small size are less likely to metastasize[2,3,18-20]. Moreover, the percentage of true occult nodal disease status among SND patients may be higher, as only routine histological examination of the neck dissection specimens was done–cutting every node in half without serial sectioning or immunohistochemistry[6]. Despite a careful preoperative risk assessment, i.e., imaging and the selection of only T1 OSCCs <15 mm in diameter and <5 mm in thickness, 13% of the WW patients still suffered from occult metastasis.

The presence of nodal disease is known to be associated with a worse prognosis[9,11]. The clinical appearance of nodal metastases during follow-up is thought to even more adversely affect DSS and OS because the disease may be more advanced when discovered[11,16,21-23]. Although comparable ECS, OS, and DSS in WW patients compared to SND patients were found in this study, it should be noted that the OSCCs of SND patients were significantly thicker and larger and showed more unfavorable histological parameters, which are all negatively associated with DSS and OS[12,24]. Despite the preoperative risk assessment on which the selection of a WW policy was based, the outcome of the more 'unfavorable' OSCCs in SND patients was comparable with the smaller and more superficial T1 OSCCs in WW patients. Moreover, significantly more ECS was encountered in WW-N+ patients, as well as a significantly worse DSS and a tendency towards worse OS, as compared to SND-N+ patients. This is probably due to the inevitable treatment delay in the WW-group–until the occult metastasis becomes visible. Although several prospective studies have described this issue[6,23,24], it is refuted by others who have found no significant differences in OS and DSS[15,16,26].

The favorable survival in SND-N+ patients may be explained by early removal of the metastasis in the resection specimen with yet less ECS. The possibility of extending the neck dissection in the case of a positive perioperative frozen section of suspected nodes may further improve neck control[27,28]. The fact that two of the three nodal recurrences in the present pN0 patients were localized at level IV supports this hypothesis. However, no significant difference in OS and DSS could be found between the extended neck dissection group and the group with only a SND, probably because of the low number of patients.

The presence of ECS is a well-known risk factor for an unfavorable outcome and warrants adjuvant chemo-irradiation, which increases morbidity[22,26,29]. From the perspective of both disease control and late morbidity, a SND could be considered in every patient with an early stage OSCC to keep the risk of treatment delay as low as possible. On the other hand, a SND may cause morbidity such as delayed wound healing, hemorrhage, infections, shoulder impairment, sensory disturbances, weakness of the marginal branch of the facial nerve, or lymph oedema[13,14]. Although in general SND morbidity is mild, performing a SND for a pN0 neck is undesirable. This indicates the need for better predictive preoperative tests and prediction models.

Future studies on sentinel node biopsy and molecular biomarkers will possibly bring a more personalized treatment strategy for OSCC patients. Based on the present data it is notable that WW-N+ patients showed a significantly higher tumor thickness as compared to WW-N0 patients (5 mm vs. 2 mm, P = 0.02). This is in accordance with others who have also found a strong correlation between tumor thickness or an infiltration depth ≥4 mm and neck node metastasis[3,25,30]. It underscores that patients with a tumor thickness ≥4 mm are at high risk of having occult nodal metastasis, as described by others[6,25]. If these patients are selected for a WW policy, they are subsequently at risk of a delay in their treatment with a higher rate of ECS and a worse DSS. The application of intraoral US scanning may prove of additional value in better predicting tumor thickness preoperatively[31]. Furthermore, incorporating imaging in the preoperative examination of the smaller and more superficial tumors may help to correctly assign patients for the WW policy. For the time being, a policy of performing an adjuvant SND in the case of pT1 tumors with a histological thickness of ≥4 mm must be applied.

In conclusion, the authors' current institutional WW policy for T1 OSCCs of <15 mm in diameter and <5 mm in thickness reduces the occult nodal rate. However, 13% were still found to suffer from nodal disease. Because WW-N+ patients showed significantly thicker OSCCs, an additional SND is advised if a histological tumor thickness ≥4 mm is found in the resection specimen (Table 2). Moreover, patients under a WW policy should be strictly monitored during follow-up, because WW-N+ patients have more ECS and an unfavorable prognosis as compared to SND-N+ patients.

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7

CHAPTER SEVEN

Oral Oncoprognostic: An accurate prognostic model to predict overall survival of squamous cell carcinoma patients

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ABSTRACT

Introduction The aim of this study was to develop an accurate prediction model and nomogram to predict five-year overall survival of post-operative OSCC patients.

Methods Four hundred and seventy-five consecutive OSCC patients who were surgically treated between 2003 and 2011 were retrospectively analyzed. Prognostic factors were associated with overall survival, after which a prediction model and nomogram for individual patients was created, called "Oral Oncoprognostic".

Results Median follow-up was 33 months (interquartile range 11 – 55 months). Five-year overall and disease-specific survival were 66% and 79% respectively. The strongest prognostic factors for overall survival were: age, synchronous primary tumor, ASA classification, primary tumor location, pathologically determined T stage, nodal stage, and extracapsular extension. The prediction model appeared well calibrated.

Conclusion Oral Oncoprognostic is a useful tool to predict overall survival in post-operative OSCC patients. The nomogram can support patient counselling and individualized treatment planning. However, external validation is necessary.

Introduction

Since many years, patients with oral squamous cell carcinoma (OSCC) are staged using the TNM (Tumor-Node-Metastasis) staging system of the Union for International Cancer Control UICC)[1]. This relatively simple system has been used successfully to plan treatment and to give an estimate on the prognosis of the individual patient. Unfortunately, this is a rough estimate as patients are categorized in heterogeneous groups in terms of demographic and histopathological variables.
In OSCC, surgical excision of the primary tumor is the preferred treatment and has the advantage of providing a resection specimen that yields important histopathological information, such as margin status and the presence of unfavorable growth parameters[2-6]. Patient demographics and these tumor characteristics are of great value for treatment decisions. However, they are not incorporated in the pre-treatment TNM staging system. Combining criteria used by the TNM staging system with patient demographics and histopathological tumor information in a prognostic model may provide valuable information that could influence the choices a physician and his patient will make regarding to possible treatment options and life in general. Moreover, important treatment decisions such as adjuvant radiotherapy, could be based on these models. In other cancers such as colorectal, urologic or breast carcinoma, prediction rules and nomograms have been widely tested and have found their way into daily clinical practice[7-10]. Still, there is little literature on prognostic models for OSCC patients. The few models that have been built did not assess important prognostic factors, such extracapsular extension and perineural growth[11-17]. Therefore, more extensive models are warranted. The aim of this study was to develop an accurate prediction model and a simple-to-use nomogram, to predict five-year overall survival for surgically treated OSCC patients.

Patients and Methods

Patients

The prospectively collected database of the Department of Oral and Maxillofacial Surgery of the University Medical Centre Utrecht was queried for all patients with a histologically confirmed OSCC of the oral tongue, upper and lower gingiva, floor of the mouth, hard palate or buccal mucosa (ICD-O-3 locations: C02.0 - C05 and C06.0 - C06.2) who were treated surgically with curative intend between November 2003 and June 2011t[18]. Patients were excluded from this study if they had in-situ carcinoma, distant metastasis or a previous head and neck cancer. Four hundred and fifty-seven patients were included in this study.

Imaging, treatment and follow-up

All patients were staged and treated according to the guideline of the Dutch Society of Head and Neck Cancer and the UICC TNM staging system(7thed.)[1, 19]. Computed tomography (CT) or magnetic resonance imaging (MRI) of the primary tumor and neck was done in all patients with cT2 tumors or higher or cT1 tumors with a clinically estimated infiltration depth of >5 mm. Mandibular invasion was assessed with a diagnostic algorithm, which consisted of CT, followed by single photon emission computed tomography (SPECT) in cases where the first scan was negative[20]. Nodal status was assessed by additional ultrasonography (US), with fine needle aspiration cytology (FNAC) on indication: FNAC was performed in case of a transverse nodal diameter > 5mm or pathological anatomy (i.e. abnormal shape or deviant architecture) of the lymph node on US. To screen for distant metastasis a chest X-ray was made in all patients and a CT-thorax in patients with cN2b with nodes in level 4 or 5, or higher N stage. The surgical procedure included a selective neck dissection (SND) of level I-III in tumors with a clinical diameter ≥ 15 mm and estimated thickness of ≥ 5 mm. A SND was omitted in tumors <15mm in diameter and <5mm in thickness, when nodal disease was not suspected on imaging or FNAC. If nodal disease was proven by FNAC or in frozen sections during SND, a SND of levels I-IV was performed only when the positive node was located in level I. In all other cases, a modified radical neck dissection (MRND) was performed. All patients classified as pN+ after their neck dissection and all those who developed neck nodal metastases during follow-up without recurrent disease at the primary site, were classified as “node positive” (N+). All others were classified as “node negative” (N–). Postoperative radiotherapy (PORT) was offered to all patients with extracapsular extension, pN2 – N3 or in case tumor was found in the resection margins and re-resection was not feasible. In case of pN1 without capsular spread in level II or III, an additional MRND or PORT was considered. Concurrent chemoradiation (with cisplatin or cetuximab in case of co-morbidity) was added in a small selection of patients. Patients over 70 years old, or patients with severe co-morbidity were excluded from systemic therapy. PORT was considered in patients with pT3-4 tumors, and when 3 or more “unfavorable” pathological parameters were present, i.e. close resection margins (1 - 3mm), non-cohesive infiltrative growth, perineural growth or vascular invasive growth. Postoperative follow-up was offered for five years with physical examination and imaging on indication.

Data collection

Prospectively gathered information from the University Medical Centre Utrecht oncology database included anonymous patient and tumor characteristics, type of treatment and follow-up details (vital status and cause of death). The Municipal Personal Records Database was used to confirm the current status of all patients.

Statistical analysis and creation of the model

Clinico-pathological characteristics are reported as frequency (percentage) for categorical variables. Continuous variables are presented as mean (standard deviation) when normally distributed or median (interquartile range (IQR)) if otherwise not. Using life table techniques, overall survival rate was calculated, illustrated by Kaplan-Meier plots. Overall survival was calculated from date of diagnosis to date of death from any cause. Multivariable Cox proportional hazards models were used to estimate the associations between prognostic factors and overall survival. A predefined set of candidate prognostic factors was chosen based on the distribution of various parameters within different groups and literature. Prognostic factors included in the "full model" were sex, age, synchronous primary tumor (absent/present), American Society of Anesthesiologists classification (ASA) classification (1-2/3-4), primary tumor site (tongue/floor of mouth/other), pathological T classification (pT1/pT2/pT3-pT4), nodal stage (N0/N1/N2-N3), surgical margins status (negative/positive), perineural growth (absent/present), and extracapsular extension (absent/present)(Table 1). ASA classification was chosen as proxy for co-morbidity because co-morbidity data were incompletely reported. To prevent losing cases due to missing values, single imputation was done for ASA classification (twelve missing cases). To prevent multicollinearity, radiotherapy was not included in the model due to significant correlation with T- and N-stage (Spearman's rank correlation coefficient 0.5; $p < 0.001$). Schoefeld residuals were used to test the proportional hazards assumption. No violation of this assumption was observed with p-values greater than 0.05. To make practical application of the model easier, backwards selection was performed. In prognostic research it is common to use a more liberal p-value than 0.05, such as 0.15[21, 22]. Hence, prognostic factors with p-value > 0.15 were manually deleted (one by one) from the full model. Bootstrapping techniques were used to adjust the regression coefficients and hazard ratios for overfitting and overoptimism[21-23]. One hundred random bootstrap samples with replacement were drawn from the dataset. The model's predictive performance after bootstrapping is the performance that can be expected when the model is applied to future comparable populations. The model was adjusted for this optimism by using the shrinkage factor. To obtain score points, the shrunken regression coefficients were divided by 0.28 and rounded. The final model was presented as a clinical prediction model. Calibration and discrimination of the model were calculated to assess the performance of the prediction model. Calibration, i.e. the extend of to which the model predictions agree with the observed probabilities, was examined by evaluating the calibration plot.

The concordance statistic (c-statistic) was calculated to assess the discriminatory power of the final model[24]. The concordance statistic is an overall measure of discriminatory power, with a value of 0.5 indicating no discrimination, and a value of 1.0 indicating perfect discrimination between those who do and those who do not experience the event of interest, i.e. death[25]. Significance level was set at $p < 0.05$. The data were analyzed using Statistical Package for Social Sciences (SPSS), version 22.0 (SPSS, Chicago, IL, USA) and the open source statistical software R-2.9.2 (R Development Core Team, 2009).

Results

Patient characteristics

Clinico-pathologic characteristics of the 457 patients in the study cohort are listed in Table 1. Forty-three per cent of patients had a pT1 tumor. Fourteen per cent of the patients had an ASA3-4 condition. Of all patients, 212 (46%) had an advanced stage of OSCC (III-IV). A neck dissection was performed in 71% of patients and in 154 patients (34%) one or more nodes were positive. Extracapsular extension was present in 53 patients (12%). Adjuvant radiotherapy was used in 202 patients (44%) of whom in three patients concurrent systemic therapy was added to the radiotherapy

Table 1. Clinicopathologic characteristics of OSCC patients (N = 457)

Characteristics	No. of patients (%)	Characteristics	No. of patients (%)
Gender		**Tumor stage**	
Male	253 (55)	I	165 (36)
Female	204 (45)	II	80 (18)
Age at diagnosis (years)		III	62 (14)
Mean (SD)	63 (12)	IV	150 (33)
Synchronous primary tumor	38 (8)	**Tumor diameter** (mm)	
ASA classification		Median (IQR)	22 (10.5-33.5)
1	129 (28)	**Tumor thickness** (mm)	
2	254 (56)	Median (IQR)	7 (2 -12)
3	62 (14)	**Growth pattern**	
Unknown	12 (3)	Non-cohesive	305 (67)
Smoking	303 (66)	Perineural	134 (29)
Alcohol	267 (58)	Vascular invasive	46 (10)
		Extracapsular	
Primary tumor site		**extension**	53 (12)
Tongue	147 (32)	**Differentiation grade**	
Floor of mouth	134 (29)	Good	48 (11)
Lower gum	71 (16)	Moderate	336 (74)
Other	105 (23)	Poor	56 (12)
Pathological T classification		Micro-invasive	17 (4)
T1	195 (43)	**Resection margins**	
T2	131 (29)	0-1 mm	56 (12)
T3	24 (5)	> 1 mm	401 (88)
T4	107 (23)	**Adjuvant radiotherapy**	202 (44)
Nodal stage		**Neck dissection**	
N0	303 (66)	None	134 (29)
N1	66 (14)	SND unilateral	188 (41)
N ≥2	88 (19)	SND bilateral	27 (6)

Abbreviations: SD, standard deviation; ASA classification, American Society of Anesthesiologists classification; IQR, interquartile range; SND, selective neck dissection; MRND, modified radical neck dissection.

Survival

The median follow-up duration was 33 months (IQR 11 – 55 months). A total of 127 patients died, of which 73 died of disease. Five-year overall survival was 66% (95% confidence interval (CI) 60 – 71%).

Nomogram

Ten candidate prognostic factors for overall survival were initially included in a Cox proportional hazards model, i.e. sex, age, synchronous primary tumor, ASA classification, primary tumor site, pathological T classification, nodal stage, surgical margins status, perineural growth, and extracapsular extension. Sex, surgical margin status and perineural growth did not add enough to the prediction of overall survival to be included in the final model. Hence, the final prediction model and nomogram included age, synchronous primary tumor, ASA classification, primary tumor site, pathological T classification, nodal stage, and extracapsular extension. Internal validation with bootstrapping techniques indicated a shrinkage factor of 0.90. Table 2 shows the final Cox proportional hazards model with shrunken β-coefficients. The prediction model appeared well calibrated as observed (Kaplan-Meier estimates) and predicted probabilities were similar (Figure 1). The optimism-corrected c-statistic was 0.77 (95% CI 0.73 – 0.81). Figure 2 shows the nomogram and five-year overall survival rates that correspond with a specific score. The nomogram facilitates calculation of the predicted five-year overall survival for an individual surgically treated OSCC patient.

Table 2. Final Cox proportional hazards model.

Prognostic factor	Value	β-coefficient*	HR	95% CI
Sex	Male	†	†	†
Age	year	0.028	1.03	1.01 – 1.05
Synchronous primary tumor	Present	0.758	2.1	1.2 – 3.8
ASA (ref: 1 - 2)	3 4	0.765	2.1	1.4 – 3.2
Primary tumor site (ref: other**)	Floor of mouth	0.047	1.0	0.7 – 1.6
	Tongue	0.485	1.6	1.0 – 2.6
Pathological T classification (ref: pT1)	pT2	0.547	1.7	1.0 – 2.9
	pT3 - pT4	1.269	3.6	2.1 – 6.1
Nodal stage (ref: N0)	N1	0.172	1.2	0.7 – 2.0
	N2 – N3	0.532	1.7	1.0 – 2.8
Surgical margin status (ref: negative)	Positive	†	†	†
Perineural growth	Present	†	†	†
Extracapsular extension	Present	0.406	1.5	0.9 – 2.6

Abbreviations: HR, hazard ratio; CI, confidence interval; ref, reference.

** To improve predictions in future OSCC patients, bootstrapping techniques were used for the β-coefficients. Shrinkage was 0.90 (optimism 0.10).*

*** Gum, retromolar area, hard palate, cheek mucosa and vestibule of mouth.*

† Prognostic factor not selected with the stepwise backward selection method.

Figure 1 Calibration plot

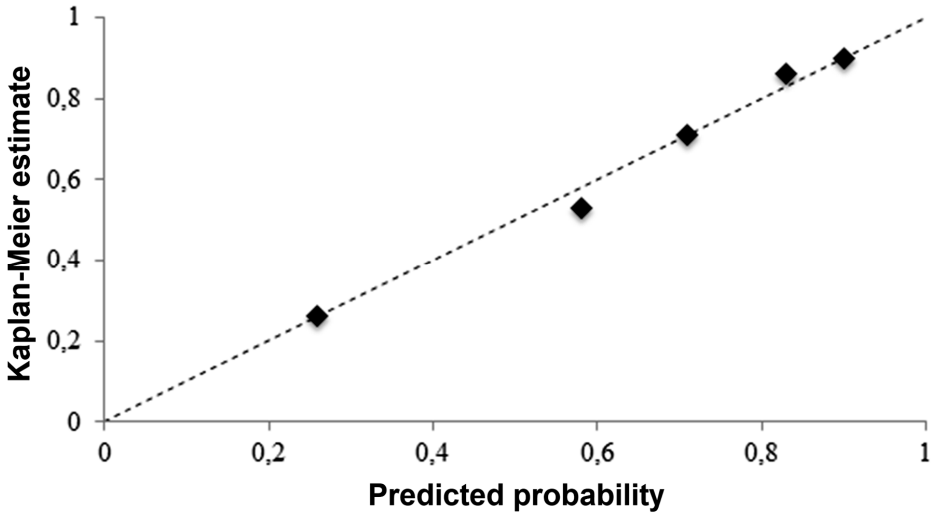
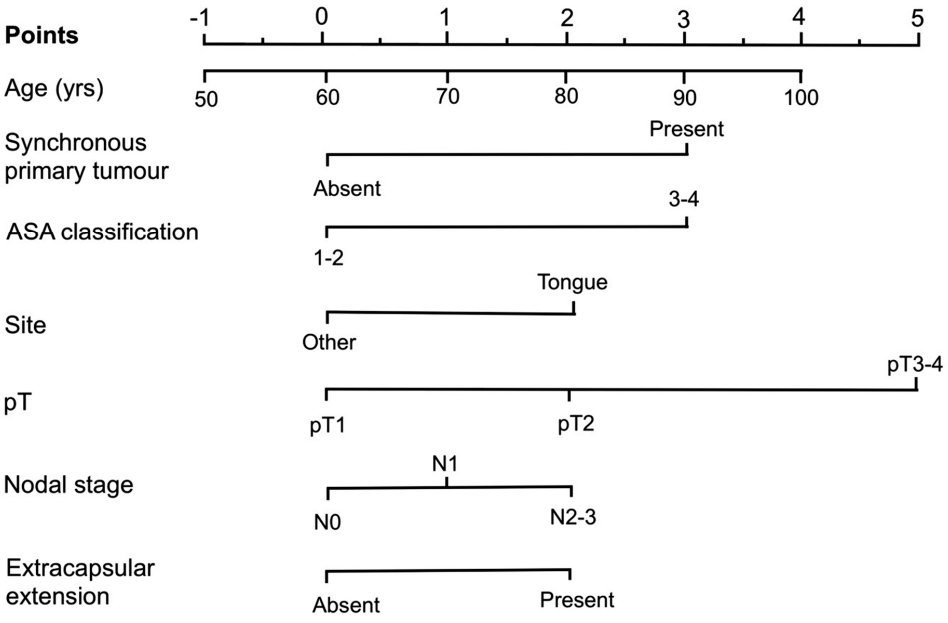


Figure 2. Nomogram and five-year overall survival rates that correspond with a specific score



Total points	< 0	0 - 1	2 - 3	4 - 5	6 - 7	8 - 9	≥ 10
Five-year OS (%)	90 - 95	85 - 90	75 - 85	60 - 75	40 - 60	20 - 40	< 20

Discussion

We developed a nomogram to estimate overall survival of individual OSCC patients who underwent surgery with or without adjuvant radiotherapy. The discriminative ability of our nomogram was reasonable and calibrated well as the predicted and observed probabilities were closely aligned.

TNM classification system

In OSCC patients determining the prognosis is mainly based on the TNM classification system[1]. which is a clear system, simple to use and therefore a very suitable tool in daily practice. The simplicity of the TNM system is at the same time it's main disadvantage: Where the TNM system remains limited to the tumors' diameter and local involvement of anatomical structures (i.e. T stage), the presence of regional metastasis and its location (i.e. N stage) prognosis can be related to several other patient- and tumor-characteristics as well.

Patient and tumor factors

Characteristics not conventionally associated with standard staging systems improved the predictive value of the nomogram. A combination of patient characteristics, age, ASA classification, synchronous primary tumor, and tumor characteristics, such as tumor site, pathological primary tumor stage, nodal stage and extracapsular extension, were incorporated in this individualized risk prediction tool. Some established prognostic factors were eventually not included in the model. Smoking and drinking status were inconsistently reported and differentiation grade was not included because its prognostic value is controversial and over 80% of the tumors are moderately differentiated. [26-28]

Other nomograms

The discriminative ability of our nomogram was reasonable with a c-statistic of 0.77. This is in line with other nomograms which had c-statistics ranging from 0.64 to 0.76[7-9]. The model was also well calibrated as the predicted and observed probabilities were closely aligned. Presence of extracapsular extension is strongly associated with worse survival but has not been included previously in a nomogram for OSCC patients[29, 30] To our knowledge, seven prediction models or nomograms concerning OSCC and OS have been published[11-17]. Frequently, patients from the same cohorts, Memorial Sloan-Kettering Cancer Centre (MSKCC) New York, Hospital AC Camargo (HACC) São Paulo, Brazil or Leiden University Medical Centre, the Netherlands, were used to build these models[11-16]. Baatenburg de Jong et al. focused on head and neck cancer in general and therefore also included sub sites such as oropharynx, nasopharynx and hypopharynx. Many of these patients did not have surgery and known prognostic factors such as extracapsular extension, perineural growth, and surgical margin status were not taken into account[11, 12, 14]. The studies of Montero et al., Gross et al., and Wang et al. also only included OSCC patients.

However, they used either loco-regional recurrence free survival as primary outcome or did not include patients receiving adjuvant radiotherapy[13, 15, 16]. Rocha et al. included 92 patients with head and neck cancer who were all treated with primary radiotherapy[17]. Due to different treatment modalities and the heterogeneity of the tumor locations, it is not possible to compare these data to our nomogram. As such, for patients with a primary surgically treated OSCC, the application of our nomogram is preferable.

Limitations

There are several limitations to this study. First, patient- and tumor-characteristics of this cohort might be unique to our practice. Although our predictive model was internally validated with bootstrapping techniques, this nomogram should be applied with caution in other populations. External validation of this nomogram is essential before incorporating it in daily practice. Second, only three patients (0.7%) were treated with postoperative chemo radiation. Nowadays, postoperative chemo radiation for patients under 70 years of age is used more frequently. It is unknown whether our nomogram is applicable to patients treated with postoperative chemo radiation. Last, we were able to assess many prognostic patient and tumor factors but unfortunately some were not available in the patient records. ASA classification was used as a proxy for comorbid medical conditions. Preferably, a validated co-morbidity index, such as the Charlson co-morbidity index or ACE27, should have been used to assess the magnitude of patients' comorbidities[31, 32]. However, in a study on free-flap reconstructions of oral cancer defects, the ASA scoring system could better predict medical complications than the Charlson co-morbidity stage[33].

Clinical value in daily practice

Primary loco-regional surgery with adjuvant radiotherapy on indication is the treatment of choice for OSCC. However, not every patient is fit enough to follow the "ideal" treatment plan. Patient specific information should be included in decision-making. An increasing number of OSCC patients is older than 65 years of age. In the Netherlands, the percentage of patients older than 65 years diagnosed with OSCC increased from 41% in 2005 to 56% in 2015[34]. In our cohort even 60% of the patients was over 65 years old. A higher age is frequently associated with multiple and more severe comorbidities[35]. Incorporation of age, synchronous primary tumors and ASA classification into a nomogram may help in decision-making. Especially in cases where we have to decide if adjuvant therapy is justifiable. For example, a 60-year-old, ASA 2 patient with a single primary pT2N1, floor of mouth OSCC without extra capsular extension would have a total sum score of three with a corresponding five-year overall survival of 75 – 85%. In comparison, an 80-year-old, ASA 3 patient with a pT1N1 squamous cell carcinoma of the tongue without extracapsular extension, would have a sum score of 8 with a corresponding five-year overall survival of 20-40%.

In case of a relative indication for PORT (i.e. close margins, in combination with ≥ 2 unfavorable pathological growth parameters) this nomogram could support the decision whether or not to perform PORT, also taking into account its side effects[36]. Disease Specific Survival was deliberately not used as end point of interest, because this nomogram had the aim to give patients insight in their overall survival. As such, it is dependent of both tumor related factors as well as co-morbidity and age. This nomogram can support in the decision whether to perform extensive multi-modality treatment given age and co-morbidity of an individual patient[19]. In the group of patients with a limited expected overall survival (i.e. elderly patients with extensive co-morbidity) the value of multimodality treatment could be placed in a more realistic perspective. Based on the nomogram, clinicians have a more evidence based ground to decide in the direction of a lighter (mono-modality) treatment i.e. only surgery or radiotherapy even though a multimodality treatment would be the treatment of first choice to reach maximal curative results. This with the goal to keep the side effects of the treatment for the individual patient as low and the benefits as high as possible.

In conclusion, this nomogram is a helpful tool to predict overall survival in post-operative OSCC patients. The nomogram can support patient counselling on individualized treatment planning in daily clinical practice. However, external validation is advised.

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CHAPTER EIGHT

General discussion and future perspectives

General Discussion and future perspectives

Maximal loco-regional tumor control with a minimum of iatrogenic side effects is the main goal in the treatment of early stage Oral Squamous Cell Carcinoma (OSCC). Thereby considering co-morbidity, age, wishes and complaints of the patient. Unfortunately, the optimal equilibrium is not found yet. Clinicians are frequently confronted with either the iatrogenic side effects of aggressive (over)treatment modalities or the lack of tumor control when a more conservative approach was chosen[1]. Since we want to reach the optimal equilibrium to improve our treatment results and at the same time minimize the side effects, thorough analysis of currently used treatment modalities is helpful. Thereby new diagnostic modalities should be explored.

The biopsy

In **chapter 2 and 3** the value of the biopsy as a predictor for histological growth parameters in the subsequent resection specimen was analyzed. We found a significant association between tumor thickness, spidery infiltrative growth (IG), perineural growth (PG) and vascular invasive growth (VG) determined on the resection specimen and nodal metastasis[1, 2]. These findings correlate with existing literature and should be considered as biological meaningful[2-4]. As a result, they play an important role in daily clinical decision making, regarding optimal (adjuvant) treatment. This clear selection of prognostic pathological parameters is the first step in order to decide which parameters determined on the biopsy specimen may eventually play a role in treatment planning. There is more debate about another frequently scored histological parameter: the determination of differentiation grade[5-9]. Differentiation grade of the biopsy and resection specimen was analyzed in **chapter 3.** We could not relate differentiation grade to the presence of nodal metastasis nor survival. Additionally, the correlation of differentiation grades between biopsy and resection specimen proved to be poor. As a result, differentiation grade of the biopsy specimen has no prognostic value concerning outcome[10]. Our findings combined with the conclusions of others underscore, that determination of histological grade on the biopsy itself is useless as a prognostic parameter for treatment planning of the neck[8, 10, 11]. One of the relevant findings in **chapter 2** is that the characteristics IG, PG and VG, found in the biopsy specimen only poorly correspond with the resection specimen. Especially the absence of growth parameters in the biopsy did not correspond with the resection specimen. This is explained by the suggestion that the biopsy dimensions are not sufficient for reliable determination of deeper situated structures (i.e. vascular and neural structures). A biopsy without unfavorable growth parameters may reassure the clinician wrongly. This is undesirable. On the other hand, the biopsy does contain a lot of tumor information. Only a biopsy diameter of more than half of the tumor diameter has a significantly higher predictive value compared to smaller biopsies. An increase of the biopsy-diameter could improve its predictive value[2].

A biopsy diameter more than half of the tumor diameter is however a rough estimation and could be exaggerated. Future research should focus on the minimal biopsy conditions: I.e. minimal size, minimal thickness and specific location of the biopsy to reliably predict specific pathological growth parameters. Meanwhile the incisional biopsy is currently only helpful in the confirmation of the clinical diagnosis “squamous cell carcinoma”. It has limited predictive value for the definite resection specimen and is therefore not suitable as a diagnostic tool for treatment planning of the neck. Alternative promising diagnostic tools such as the sentinel node biopsy, the use of biomarkers and Ultra Sound guided tumor thickness measurements deserve attention as they may add significant predictive knowledge and contribute to a more patient specific treatment planning of the neck[12-16].

The pathology report

Margin status, the presence of IG, PG, VG and bony invasion (BI) are important determinants that guide further treatment[6, 17, 18]. The pathological scoring of growth parameters in the tumor is more and more done on digital slides hence information about inter observer variation (IOV) of pathological assessment on digital slides is relevant. In **chapter 4**, only a moderate agreement for BI (kappa 0.475), a fair agreement for PG (kappa 0.223) and even only a slight agreement for IG (kappa 0.100) was reached between six dedicated pathologists of university head and neck centers is the Netherlands. This is not only a problem of a local group of pathologists, as in literature poor IOV in scoring of pathological parameters for head and neck cancer is reported before[19, 20]. For instance, scoring of the pattern of invasion resulting in kappa’s between 0.193 and 0.580 which is at most a moderate agreement[21, 22]. Our findings are a confirmation of this problem and demonstrate the necessity for improvement of scoring results among pathologists. Since the mentioned IOV studies where performed on analogue slides it is questionable if the use of digital H&E slides is responsible for the high IOV in this study. That seems unlikely. Most probably, not the digital slides but the pathologist’s experience, the nature of the parameters, the definitions and interpretations are crucial factors in the judgement of pathology slides[23]. The application of digital H&E sections is actually beneficial: digital slides don’t take up any physical space and peer consultations are faster and more efficient because of the limitless availability of the H&E sections worldwide[23]. Furthermore, the use of digital slides provides the opportunity to explore novel techniques like deep learning by artificial intelligence, already studied in other fields of oncology like hematological and lung malignancies [24, 25]. If clinicians want to use the pathology report as a leading tool for adjuvant treatment, IOV on parameters scored should be reduced.

First, clear and transparent definitions in quality of screens and screen settings as well as establishing clear definitions for the different histological parameters by regular consensus meetings may contribute to a better reproducibility[22, 26]. Secondly novel techniques like pattern deep learning by artificial intelligence should be embraces and explored. They can potentially support the pathologist in the future and may reduce inter-observer variation[24, 25].

Resection margins

In **chapter 5,** the problem of local recurrence was analyzed. In this study, the number of local recurrences is with 4.5% on the lower bound of recurrences mentioned in literature[27-29]. This suggest that the used treatment protocol is successful. Still local recurrence occurs, and since it is a strong prognostic factor, it should be reduced to a minimum[18, 30]. Due to the low number of recurrences, consequently there is an impossibility to reach significance in finding a relation between margin status, histological parameters or adjuvant treatment modality and local recurrence. This is a well-known problem in literature[29, 31]. Conclusions drawn, in the existing literature, regarding local residual disease should be placed in this perspective. A multicenter approach could be a solution. However, inclusion of patients from different head and neck centers will certainly lead to a more heterogeneous study population regarding epidemiologic characteristics, treatment protocols, primary and/or adjuvant operation techniques and adjuvant radiation schedules. Besides the low number of recurrences selection bias is another important factor in retrospective analyses, which makes it impossible to draw final conclusions about the preferred adjuvant treatment. Mostly patients with an unfavorable tumor are treated with post operative radiotherapy (PORT). Due to the selection bias in this material also the preference for a local re-resection, watchful waiting or PORT could not be ascertained. Comparison of patients within the watchful waiting group proved to be possible. Regarding local recurrence, it revealed that resection margins ≥3 mm with ≤ 2 unfavorable growth parameters are as safe as margins > 5mm. This finding enables us to refrain patients from adjuvant treatment and its additional morbidity in selected cases with clear margins <5mm. It is questionable if margin status on itself should be the key parameter to determine the necessity for adjuvant treatment[17, 32, 33]. Others stated already that resection margins >5mm can just as well lead to local recurrence [31, 34]. Besides the margin status, the focus should predominantly be put on the identification of specific risk factors concerning local recurrence. Moreover, there is the problem of a new primary versus a local recurrence in areas of oral field cancerization[30]. True recurrences tend to occur in the deep margins, whereas recurrent cancer at an adjacent mucosal site even with an identical clonality, might very well be a new tumor. Especially when mild dysplasia was found in epithelial resection margins[30, 35].

A multicenter approach preferably in a prospective setting, would be of additional value, focusing on the watchful waiting group after primary resections of small tumors. Analysis of the presence of the conventional “unfavorable” pathological growth parameters[33] and more fundamental risk parameters (i.e. molecular genetic factors) in patients with local recurrences could create a more specific risk profile. More understanding of tumor biology may lead to a more tumor specific personalized treatment. In the meantime, a meta-analysis of available literature to identify reliable prognostic factors could create a useable risk profile. These findings can guide the further set up of a prospective multicenter approach.

The neck

In general, three different approaches for the clinically negative neck in oral cancer are possible: The sentinel node biopsy (SNB), a selective neck dissection level I II and III (SND) or watchful waiting of the neck (WW). One of the main findings in **chapter 6** is that 29% of the SND patients and only 13% of WW patients had occult nodal disease (N+). Patients were assigned to a WW policy in case of small cT1 tumors (i.e. clinical diameter <15mm and estimated infiltration depth < 5mm) and if no nodal disease was suspected on imaging or FNAC. Tumor thickness is proved to be related to nodal metastasis[3, 36]. In this study, patients in the WW group with occult metastasis (WW-N+) showed indeed thicker tumors as compared to WW patients without occult metastasis (WW-N0) patients: 5 mm versus 2 mm, P= 0.02. This finding underscores that tumor thickness – or invasion depth - should be regarded as an important prognostic determinant. The adjustments in the recent TNM 8th edition meet these findings by incorporation tumor invasion depth as a direct factor influencing T stage[37]. More knowledge of tumor thickness in advance would be of added value. US guided tumor thickness measurements could contribute to provide more information besides the already used imaging modalities as MRI and or CT[38]. Information about tumor thickness based on the biopsy specimen is known to be unreliable[2]. Another important finding is that patients in the WW group with appearance of initially occult metastasis during follow up (WW-N+), showed significantly more Extra Capsular Spread (ECS) as compared to patients in the selective neck-dissection group with occult metastasis (SND-N+) (56% vs. 14%, P = 0.016) and had a significantly worse 3-year Disease Specific Survival (DSS) than SND-N+ patients (56% vs. 82%, P= 0.02). This underscores that progression of nodal growth indeed results in the increase of ECS. The determinant ECS is meanwhile recognized as an important prognostic factor and now directly influences the TNM stadium in the new TNM 8th edition[37]. We concluded that for small oral cancers, a WW policy is acceptable if tumor thickness proves to be <4 mm. Otherwise, an additional treatment of the neck is advised since WW-N+ patients show more ECS, with a worse DSS than SND-N+ patients. With the upcoming incorporation of the sentinel node biopsy (SNB) in more and more head and neck centers this statement can be argued[39, 40]. Application of the SNB will reduce invasiveness compared to a SND and identifies more occult metastasis compared to conventional staging techniques[39, 41, 42].

Thereby it identifies aberrant drainage patterns and detects potential metastasis in unexpected levels contra-lateral or lower levels[43]. Still 6 % of the sentinel lymph node negative patients will be confronted with overt metastasis during follow up[40]. The sentinel node biopsy (SNB) has its disadvantages. First, still around 70% of the patients receive an invasive treatment of the neck without true evidence for metastasis. Secondly for floor of the mouth tumors a reliable SNB procedure is more difficult because of the “shine-through” phenomenon of the tracer around the primary tumor that potentially hides the positive lymph nodes in vicinity[39, 43, 44]. Although the super-selective neck dissection of the pre-glandular level I-triangle seems to render favorable results (i.e. a false-negative rate of 8% with a negative predictive value of 96.4%)[45]. Thirdly, in case of a positive SNB an additional neck-dissection is necessary, often as a 2nd stage procedure, with a potential treatment delay and technical difficulties because of early scar formation. In this perspective, for SNB-positive patients, a higher risk of nodal recurrence with a worse prognosis compared to SNB negative patients is described with less options for salvage surgery[39]. In general, reducing overtreatment in case of node negative patients and under-treatment in case of true metastasis remains an issue with developments still in progress. In this perspective it is still eligible not to touch the neck at all if the risk of occult metastasis is low. One option is to refrain from invasive treatment of the neck in the most small and superficial OSCC’s (<2mm). In clinical practice these patients often already had an excisional biopsy in local anesthesia. To explore this suggestion a, more fundamental genetic research to understand tumor biology is essential. A combination of clinical findings (i.e. tumor infiltration depth) and molecular observations of the primary tumor[46, 47] may eventually lead to further optimize this equilibrium.

Prognosis and TNM 8th edition

The TNM classification system is the currently used tool to estimate prognosis. However specific patient demographics and histo-pathological tumor characteristics are not incorporated in the system[37, 48]. The determination of the prognosis of surgically treated oral cancer patients is of great value in daily practice. Our nomogram “oral oncoprognostic” was built with this goal. A combination of patient characteristics, age, ASA classification, synchronous primary tumors, and tumor characteristics, such as tumor site, pathological primary tumor stage, nodal stage and extra-capsular extension, were incorporated in this individualized risk prediction tool. Some established prognostic factors like perineural growth and margin status of the primary tumor[3, 17, 18], were eventually not included in the model since they did not add enough to the prediction model to be included in the final model. Smoking and drinking was inconsistently reported and where hence not added to the model. DSS was deliberately not used as end point of interest, because this nomogram had the aim to give patients insight in their overall survival. As such, it is dependent of both tumor related factors as well as co-morbidity and age.

The simplicity of the TNM 7 system[48] was a disadvantage. Where the TNM 7 system remains limited to the tumors' diameter and local involvement of anatomical structures (i.e. T stage), the presence of regional metastasis and its location (i.e. N stage) prognosis can be related to several other patient- and tumor-characteristics as well. With the introduction of the TNM 8th edition[37] important factors related to prognosis as extra nodal spread and tumor infiltration depth where incorporated in the TNM system which makes it a more accurate predictor. Our nomogram is still based on the TNM 7th edition. In consequence, the nomogram is not accurate any more when used in combination with the current TMN 8. However, factors as tumor location, age, co-morbidity and the presence of a synchronous primary tumor are not incorporated in the TNM 8 system. Hence this nomogram is still of added value and can support in the decision whether to perform extensive multi-modality treatment given age and co-morbidity of an individual patient[49]. It should be emphasized that the TNM 7th edition should be used for the nomogram than. In the group of patients with a limited expected overall survival (i.e. elderly patients with extensive co-morbidity) the value of multimodality treatment could be placed in a more realistic perspective. Based on the nomogram, clinicians have a more evidence-based ground to decide in the direction of a lighter (mono-modality) treatment i.e. only surgery or radiotherapy even though a multimodality treatment would be the treatment of first choice to reach maximal curative results. This with the perspective to keep side effects of the treatment for the individual patient as low and the benefits as high as possible in their remaining life. Because of the additional value of this nomogram in daily practice an adaptation of the oral oncoprognostic algorithm to the TNM 8 is expected to be of use. Our future focus will lay in adjustment of the nomogram to make it suitable for use in combination with the TNM 8th edition.

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9

CHAPTER NINE

Summary

This thesis addresses some key topics that play a central role in frequent discussions during the treatment of early stage oral squamous cell carcinomas.

The biopsy

In oral squamous cell carcinoma (OSCC), the presence of unfavorable histological growth parameters; tumor infiltration depth, perineural growth (PG), vascular invasive growth (VG) and spidery infiltrative growth (IG) are associated with aggressive tumor behavior, with a higher risk for regional metastasis and therefore a worse prognosis. Until now, these histological parameters are mainly scored on the final resection specimen. Treatment decisions concerning the neck have already been made by then. Reliable information about these histological parameters from a biopsy in advance could be of importance in decision-making concerning the neck. In **chapter 2,** the value of the biopsy, as a predictor for the presence of unfavorable histological growth parameters in the subsequent resection specimen, was analyzed. In this study the final resection specimen was considered as the golden standard. To estimate the relation of unfavorable histological parameters with the occurrence of metastasis, and to determine the predictive value of the biopsy, the following items where addressed:

1. The presence of the histological growth parameters PG, VG and IG, as determined on the resection specimen, was related to occult metastasis and survival.
2. The predictive value of the biopsy was determined by analyzing the correlation between the biopsy and the subsequent resection specimen, concerning the determination of PG, VG and IG.
3. Determination of tumor infiltration depth based on the biopsy was tested on reliability.
4. The predictive value of the biopsy was related to the diameter of the biopsy.

In total 149 patients with a pT1-2 cN0 OSCC of the tongue, floor of mouth or cheek where included.

-Patients with occult metastasis showed significantly more PG, VG and IG in the resection specimen ($p=0.02$, $p=0.001$, and $p=0.001$, respectively). No correlation could be demonstrated between the presence of PG, VG and IG on the biopsy and occult metastasis or survival.
-For PG, VG and IG, a similar result between biopsy and resection specimen was found in resp. 77%, 90% and 71% of the cases. The diagnostic gain of a biopsy containing PG, VG and IG was respectively 57%, 40% and 19%. The diagnostic gain of a biopsy negative for PG, VG and IG was low, resp. 2%, 0% and 22%.
-Tumor infiltration depth could be estimated reliably in only 15% of the cases.
-The predictive value of the biopsy significantly improved in case of a biopsy diameter more than half of the tumor diameter ($p=0.03$).

Conclusions chapter 2

-The histological growth parameters PG, VG and IG determined on the resection specimen could be related to the presence of occult metastasis. These parameters have in consequence prognostic value.
-There is a poor correlation between histological parameters determined on the biopsy and resection specimen. Especially biopsies that lack a specific histological parameter are not reliable and can reassure the clinician wrongly.
-Reliable determination of tumor infiltration depth is not possible in the majority (85%) of cases because the biopsy thickness does not comprise the tumor thickness.
-Increase of the biopsy diameter by ≥ half of the tumor diameter, could improve the predictive value of the biopsy.
-In this group of patients, the biopsy does currently not add any value in the treatment planning of the cN0 neck.

In case of an OSCC a distinction is made between well, moderately, poorly and undifferentiated tumors. In many head and neck cancer centers the biopsy specimen as well as the resection specimen is routinely graded. Deterioration of grade is related to aggressive tumor behavior and metastasis. This relation is controversial however. In **chapter 3** the value of the biopsy as a predictor for the differentiation grade in the subsequent resection specimen was analyzed. To analyze if grading of OSCC's on the biopsy and resection specimen is of added value the following topics were covered:

1. The relation between differentiation grade, determined on the biopsy- and resection specimen, and the occurrence of occult metastasis and survival was determined.
2. The predictive value of the biopsy was determined by analyzing the correlation between biopsy and resection specimen concerning the determination of differentiation grade.
3. Deterioration of grade determined on the resection specimen was related to the presence of PG, VG and IG.
4. The effect of adding IG to the differentiation grade on the correlation with the N stadium, was analyzed.

In total 145 patients with a pT1-2 cN0 OSCC of the tongue, floor of mouth or cheek were included.

-Deterioration of differentiation grade on the biopsy- as well as the resection specimen was not related to the presence of occult metastasis (resp. p=1.0 and p=0.50) nor to survival (resp. p=0.65 and p=0.44).
- Correlation between biopsy and subsequent resection specimen concerning differentiation grade is poor. A similar differentiation grade in biopsy- and resection specimen considering well, moderately and poorly differentiated tumors, was found in resp. 43%, 83% and 39% of the cases.

-Only in case of poorly differentiated tumors, a significantly higher amount of VG was found (p=0.02). No significant relation could be found between the presence of the unfavorable histological parameters PG and IG and the deterioration of differentiation grade (resp. p=0.15 and p=0.85).
-Only the combination of IG with a moderately differentiation grade gave a significantly higher risk on nodal metastasis (p=0.02).
Combining the pattern of invasion with well and poorly OSCC's did not lead to a significantly higher risk on nodal metastasis (resp. p=0.62 and p=0.47).

Conclusions chapter 3
-Concerning the poor correlation of differentiation grade between biopsy and resection specimen, the differentiation grade determined on the biopsy must be considered as a poor predictor for the subsequent resection specimen.
-Since deterioration of the differentiation grade could not be related to the presence of nodal metastasis nor survival, these criteria don't have any prognostic value concerning outcome and are consequently of little value for treatment planning.
-By adding the histological parameter IG to the differentiation grade, the prognostic value could increase, probably because it is an independent risk factor for nodal metastasis.

The pathology report

In case of an OSCC the pathology report is a dictating tool whether to perform an adjuvant therapy after primary surgery. Pathologists assess more and more on digital slides. Since the pathology report is a determining factor, knowledge about the inter-observer variation (IOV) is relevant to estimate the level of reliability and reproducibility of the report. In **chapter 4** the pathology report was highlighted. The focus was on the IOV during the determination of the histological parameters: bony invasion (BI), perineural growth (PG), Vascular invasive growth (VG) and Spidery infiltrative growth (IG) on digital H&E slides of the resection specimen.

Digital H&E slides were re-assessed on the presence of unfavorable histological growth parameters by 6 dedicated head and neck pathologists. The IOV between these pathologists was determined.
-For BI, the inter observer concordance varied between 73% and 100% with a Fleiss'Kappa of 0.457 ($p<0.001$) which is called a moderate inter-observer agreement.
-For IG, the inter observer concordance varied between 39% and 79% with a Fleiss'Kappa of 0.100 ($p<0.001$) which is called a slight inter-observer agreement.
-For PG, the inter observer concordance varied between 33% and 97% with a Fleiss'Kappa of 0.223 ($p<0.001$) which is called a fair inter-observer agreement.

Conclusions chapter 4
-With at most a moderate inter observer agreement during the assessment of digital H&E slides on the presence of unfavorable histological parameters, the current reproducibility is not reliable enough to guide adjuvant treatment planning.
-Improvement of the IOV concerning the assessment of unfavorable histological parameters in OSCC is mandatory.
-If clinicians want to believe that unfavorable histological parameters are of importance in treatment planning, better reproducibility is warranted. Clear and transparent definitions in quality of screens and screen settings as well as establishing clear definitions for the different histological parameters by regular consensus meetings may contribute.
-This study could serve as a baseline, to evaluate the effect of future training and consensus meetings.

Resection margins

An OSCC is preferably removed with a pathologically free margin >5mm (FM) in which case local adjuvant treatment is not indicated. When tumor cells are present in the resection margin there is a pathologically positive margin (PM). In general this is an indication for adjuvant treatment. In case of free resection margins with tumor cells close to the border (<5mm) there is a close margin (CM). In case of close margins discussion arises about the necessity for adjuvant treatment. Then there often is a lack of consensus if and which adjuvant treatment to choose. **Chapter 5** focused on local residual disease.

1. The occurrence of local residual disease after primary resection of an OSCC of the tongue, floor of mouth or cheek was analyzed.
2. The occurrence of local residual disease was related to margin status, the presence of unfavorable histological parameters (PG, VG, IG) and the type of adjuvant approach (i.e. follow up, re-resection or postoperative radiation therapy (PORT)).
3. Follow-up patients with a FM and a follow-up patients with a CM (≥3mm <5mm) where compared.
4. Three year overall and disease specific survival where determined and related to margin status.

In total 200 patients with a stage I-II OSCC of the tongue, floor of mouth or cheek where included.

-Of the 200 patients 11% had a PM, 63% a CM and 26% a FM.
-Nine out of 200 patients (4.5%) had local recurrent disease.
-One recurrence was found in the re-resection group, 5 in the PORT group and 3 in the follow-up group.
-Two recurrences where found in the PM, 5 in the CM and 2 in the FM group.
-Because of the small numbers, no significant relation could be found between local recurrence and margin status as well as local recurrence and unfavorable histological parameters.
Because of the same reason no preference for local adjuvant therapy could be estimated.
-No significant differences in recurrence and overall survival were seen between the follow-up group with FM and the follow-up group with CM ≥3mm and ≤2 unfavorable histological parameters. (p=0.57).
-No significant differences in overall and disease specific survival were seen between the FM, CM and PM group.

Conclusions chapter 5

-In our current treatment protocol, the chance of developing local recurrent disease was low (4,5%) regardless of margin status.

-Based on this study, there is no evidence for one adjuvant treatment modality above another.

-Concerning local recurrence for T1-2 tumors, no evidence was found for the need for adjuvant treatment in case of margins ≥3mm and ≤2 unfavorable histological parameters: A clear margin of ≥3mm is as safe as ≥5mm.

- Regarding side-effects in these circumstances, it is incorrect to add therapies like re-resection or PORT in case of clear margins ≥3mm.

The neck

The presence of cervical metastasis is an important prognostic factor concerning survival in patients with an OSCC. With our current primary staging techniques (Ultra Sound in combination with CT and/or MRI) around 20-40% of the metastasis is missed. **In chapter 6** the occurrence of neck nodal metastasis of stage I-II OSCC patients was analyzed. Two treatment strategies were evaluated. The selective neck dissection levels I II III (SND) or watchful waiting (WW). In case of a SND the patient is invasively treated with potential peri-operative morbidities as a result. In case of watchful waiting (WW) of the neck, there is a chance that occult metastases appear during follow up with a treatment delay in consequence. To gain insight in the consequences of the different approaches, the following topics were analyzed:

1. The distribution of occult metastasis over the different treatment groups.
2. The presence of extra capsular spread.
3. The presence of unfavorable histological parameters in the resection specimen of patients with (N+) and without (N-) occult metastasis in the WW and SND group.
4. Differences in three years overall survival (OS) and disease specific survival (DSS) between the two treatment strategies.

In total 193 patients with a stage I-II OSCC of the tongue, floor of mouth or cheek were included.
In patients with an estimated tumor-diameter <15mm and an infiltration depth of <5mm only the primary tumor was resected. The neck was closely followed up (WW-group). The other patients received also a selective neck-dissection level I II III (SND group).

-Forty-five out of 193 patients (23%) had an occult metastasis (N+).
-Thirty-six out of 123 SND patients (29%) and 9 out of 70 WW patients (13%) where N+.
-At least 4% of the patients in the SND-N+ group showed extra capsular spread.
-At least 7% of the patients in the WW-N+ group showed extra capsular spread.
-WW-N+ patients had a significantly higher infiltration depth compared to WW-N- patients. No significant differences were seen for other histological parameters between these groups.
-Between the SND and WW group no significant differences were seen in OS resp. 90% vs 86% (p=0.54).
-The SND-N+ group had a significantly better DSS compared to the WW-N+ group 82% vs 56% (p=0.02). No differences were seen in OS between these groups.

Conclusions chapter 6

-The policy to select patients with an estimated tumor diameter <15mm and infiltration depth <5mm for close follow up of the neck, reduces the chance of having occult metastasis from 23% to 13% in patients with a stage I-II OSCC.

-Unless primary staging and careful selection still 13% of the patients in the WW group had occult metastasis and is undertreated.

-WW-N+ patients had a significantly higher infiltration depth compared to WW-N- patients, hence we advise a SND in case of an infiltration depth >4mm.

-Careful follow-up of the neck is mandatory in the WW group because WW-N+ patients showed more extra capsular growth and a worse DSS compared to SND-N+ patients.

Prognosis

Clinicians have a broad range of treatment options for patients with an OSCC. Patients are getting older and the relevance of patient participation in deciding on their treatment is increasing. This urges to adept the most effective cancer therapy to the most eligible therapy, with age, co-morbidity and wishes of the individual patient taken into concern. In **Chapter 7** prognosis is the main topic. The aim of this study was to develop an accurate prediction model and nomogram to predict five-year overall survival of post-operative OSCC patients to support in shared decision making. Four hundred and seventy-five consecutive OSCC patients who were surgically treated between 2003 and 2011 were retrospectively analyzed. Prognostic factors were associated with overall survival, after which a prediction model and nomogram for individual patients was build, called “Oral Oncoprognostic”. The strongest prognostic factors for overall survival were: age, synchronous primary tumor, ASA classification, primary tumor location, pathologically determined T stage, nodal stage, and extracapsular extension.

Conclusions chapter 7

Oral Oncoprognostic is a useful tool to predict overall survival in post-operative OSCC patients. The nomogram can support patient counselling and individualized treatment planning. However, adjustment to the TNM 8th edition and external validation is necessary.

10

CHAPTER TEN

Samenvatting

Dit proefschrift behandeld enkele sleutel onderwerpen die een centrale rol spelen in terugkomende discussies tijdens de behandeling van het vroeg stadium plaveiselcelcarcinoom.

Het biopt

In geval van een oraal plaveiselcelcarcinoom (OPCC) zijn tumor infiltratie diepte, Perineurale Groei (PG), Vaso invasieve Groei (VG) en Sprieterige Infiltratieve Groei (IG) histologische kenmerken geassocieerd met agressief tumor gedrag. Als gevolg hiervan bestaat er een hogere kans op regionale metastasering en derhalve een slechtere prognose. Tot op heden werden deze kenmerken hoofdzakelijk bepaald op het resectie preparaat. Er is dan vaak al een besluit genomen met betrekking tot de behandeling van de hals. Kennis over deze “ongunstige” groeikenmerken vóór aanvang van de primaire therapie zou van invloed kunnen zijn op de behandeling van de hals. In **hoofdstuk 2** werd gekeken naar de waarde van het biopt als voorspeller van ongunstige pathologische groeikenmerken in het resectie preparaat. In deze studie werd het resectie preparaat als gouden standaard beschouwd. Om de relatie van de groeikenmerken met het optreden van metastasen, en de voorspellende waarde van het biopt te kunnen bepalen zijn een aantal onderwerpen belicht.

1. Er werd gekeken of groeikenmerken (PG, VG, IG) bepaald op het resectie preparaat en het biopt gerelateerd konden worden aan de aanwezigheid van halsklier metastasen en overleving.
2.De voorspellende waarde van het biopt werd bepaald door te kijken of groeikenmerken bepaald op het biopt overeenkwamen met de groeikenmerken bepaald op het resectie preparaat.
3. Er werd gekeken of de tumor infiltratiediepte betrouwbaar kon worden bepaald aan de hand van het biopt.
4. Er werd gekeken of de voorspellende waarde van het biopt samenhangt met de diameter van het biopt.

In totaal werden 149 patiënten met een pT1-2 cN0 OPCC van de tong, mondbodem of wang geïncludeerd.

-Bij patiënten met een metastase werd significant meer PG, VG en IG gezien in het resectie preparaat. (P = 0.02, P = 0.001, en P = 0.001, resp.) Er werd geen correlatie aangetoond tussen de aanwezigheid van PG, VG en IG in het biopt en halsklier metastasen of overleving.
-Voor PG, VG en IG werd in resp.77%, 90% en 71% een gelijk resultaat tussen het biopt en het resectie preparaat gevonden. De diagnostische winst van een biopt positief voor PG, VG en IG was resp. 57%, 40%, en 19%. De diagnostische winst van een biopt negatief voor PG, VG en IG was laag, resp. 2%, 0% en 22%.
-De tumor infiltratie diepte kon in 15% van de patiënten betrouwbaar worden bepaald.
-De voorspellende waarde van het biopt bleek significant hoger bij een biopt diameter meer dan de helft van de eigenlijke tumor diameter (p=0.03).

Conclusies hoofdstuk 2
-De groeikenmerken PG, VG en IG bepaald op het resectie preparaat konden worden gerelateerd aan het voorkomen van occulte metastasen en zijn daarom van prognostische betekenis.
-Er bestaat een slechte correlatie tussen groeikenmerken bepaald op het biopt en het resectie preparaat. Vooral biopten negatief voor een bepaald groeikenmerk, zijn niet betrouwbaar, en kunnen de behandelaar onterecht geruststellen.
-Tumor infiltratiediepte is in de meeste gevallen (85%) niet betrouwbaar te bepalen op het biopt, omdat de biopt dikte de tumor infiltratie diepte niet overschrijdt.
-Vergroten van de biopt diameter tot ≥ de helft van de tumor diameter kan leiden tot een betere voorspellende waarde van het biopt.
-Het biopt in de huidige vorm is niet van meerwaarde in de behandel planning van de cN0 hals.

Bij het OPCC wordt onderscheid gemaakt tussen goed, matig, slecht en ongedifferentieerde tumoren. De differentiatiegraad wordt in veel hoofd hals centra routinematig bepaald op zowel het biopt als het resectie preparaat. Het verslechteren van de differentiatiegraad wordt gerelateerd aan agressiever tumor gedrag en metastasering. Deze relatie is echter controversieel. In **hoofdstuk 3** werd het biopt als voorspeller van de differentiatiegraad aanwezig in het resectie preparaat belicht. Om te kijken of het graderen van OPCC's op biopt en resectie preparaat van meerwaarde is werd gekeken naar een aantal onderwerpen:

1. Er werd gekeken of de differentiatiegraad bepaald op het resectie preparaat en het biopt gerelateerd konden worden aan de aanwezigheid van halsklier metastasen en overleving.
2.De voorspellende waarde van het biopt werd bepaald door te kijken of de differentiatie graad bepaald op het biopt overeenkwam met de differentiatie graad bepaald op het resectie preparaat.
3. Er werd gekeken of de verslechtering van de differentiatiegraad in het resectie preparaat te relateren is aan het voorkomen van de ongunstige groeikenmerken PG, VG en IG.
4. Er werd gekeken of het toevoegen van IG aan de gradering leidt tot een betere correlatie met het N-stadium.

In totaal werden 145 patiënten met een pT1-2 cN0 OPCC van de tong, mondbodem of wang geïncludeerd.

-Het verslechteren van de gradering op zowel het biopt als het resectie preparaat kon niet worden gerelateerd aan de aanwezigheid van occulte metastasen (resp. p=1.0 en p=0.50) en overleving (resp. p=0.65 en p=0.44).

-Er bestaat een slechte correlatie tussen het biopt en het resectie preparaat aangaande de differentiatiegraad. Een gelijk resultaat voor goed, matig en slecht gedifferentieerd tumoren werd gevonden in respectievelijk 43%, 83% en 39% van de gevallen.
-Alleen in geval van slecht gedifferentieerde tumoren werd significant meer vaso-invasieve groei gevonden (p=0.02). Er werd geen significante relatie gevonden tussen het voorkomen van de ongunstige groeikenmerken PG en IG en het verslechteren van de gradering (resp. p=0.15 en p=0.85).
-Het toevoegen van IG aan de gradering leidt in geval van matig gedifferentieerde tumoren tot een significante relatie met het N-stadium (p=0.02). Bij goed slecht en ongedifferentieerde tumoren wordt geen significantie gezien (resp. p=0.62, p=0.47).

Conclusies hoofdstuk 3
-Er bestaat een slechte correlatie tussen biopt en resectie preparaat aangaande gradering. Derhalve is het biopt te beschouwen als een slechte voorspeller voor het definitieve resectie preparaat.
-Omdat het verslechteren van de differentiatiegraad niet kon worden gerelateerd aan de aanwezigheid van metastasen of overleving, lijkt de gradering geen prognostische waarde te hebben en is niet van meerwaarde in de behandel planning.
-Door het toevoegen van het groeikenmerk IG aan de gradering kan de prognostische waarde verbeteren. Waarschijnlijk omdat IG een onafhankelijke voorspeller is voor occulte metastasen.

Het pathologie verslag

Bij een OPCC is het pathologie verslag voor een groot deel bepalend in de keuze om al dan niet aanvullend te behandelen na primaire chirurgische therapie. De beoordeling wordt meer en meer uitgevoerd op digitale coupes. Aangezien het verslag een bepalende factor is, is kennis over de inter-observer variatie (IOV) van groot belang om de betrouwbaarheid en dus ook reproduceerbaarheid in te kunnen schatten. In **hoofdstuk 4** werd er gekeken naar de IOV tussen pathologen bij de beoordeling van de histologische (groei)kenmerken botinvasieve groei (BI), Perineurale Groei (PG), Vaso invasieve Groei (VG) en Sprieterige Infiltratieve Groei (IG) op digitale H&E coupes van het resectie preparaat.
Digitale H&E coupes werden door 6 hoofd hals pathologen uit 6 verschillende hoofd hals centra in Nederland beoordeeld op de aanwezigheid van “ongunstige” histologische groeikenmerken.

-Voor BI varieerde de inter-observer concordantie tussen 73% tot 100% met een Fleiss’ Kappa van 0.457 ($p<0.001$) wat een gemiddelde inter-observer overeenkomst genoemd wordt.
-Voor IG varieerde de inter-observer concordantie tussen 39% en 79% met een Fleiss’ Kappa van 0.100 ($p<0.001$) wat een geringe inter-observer overeenkomst genoemd wordt.
-Voor PG varieerde de inter-observer concordantie tussen 33% en 97% met een Fleiss’ Kappa van 0.223 ($p<0.001$) wat een redelijke inter-observer overeenkomst genoemd wordt.

Conclusies hoofdstuk 4
Met hoogstens een gemiddelde overeenkomst tussen pathologen bij het beoordelen van digitale H&E coupes op ongunstige groeikenmerken is de huidige reproduceerbaarheid niet betrouwbaar genoeg en kunnen de bevindingen niet worden gebruikt om de adjuvante behandelplanning in de dagelijkse klinische praktijk te begeleiden. Verbetering van IOV is noodzakelijk.

Als clinici willen vasthouden aan de overtuiging dat ongunstige histologische parameters van belang zijn in de behandelplanning, kunnen duidelijke en transparante definities van de kwaliteit van schermen en scherminstellingen en duidelijke definities voor de verschillende histologische parameters door regelmatige consensusbijeenkomsten bijdragen aan een betere reproduceerbaarheid.
Deze studie kan als basis dienen om het effect van toekomstige trainings- en consensusbijeenkomsten te evalueren.

Resectie marges

Een OPCC wordt bij voorkeur verwijderd met een pathologische vrije marge van >5mm (VM). Lokale nabehandeling is dan niet geïndiceerd. Indien tumorcellen in de resectie randen aanwezig zijn is er sprake van een ir-radicale resectie, een positieve marge (PM). Er is dan doorgaans een indicatie voor een aanvullende behandeling. In geval van vrije resectie randen, echter <5mm, een krappe marge (KM), is er discussie over de indicatie van een aanvullende behandeling. Naast de discussie of er aanvullend behandeld moet worden is er niet zelden gebrek consensus over de te kiezen aanvullende behandeling. In **hoofdstuk 5** werd het probleem “lokaal recidief” geanalyseerd. Om meer inzicht te krijgen in de rol van resectie marges, en het onderbouwen van het al dan niet toepassen van aanvullende therapieën, werden de volgende onderwerpen belicht.

1.Het voorkomen van lokaal recidief na primaire resectie van een OPCC van de tong, mondbodem of de wang.
2.Het voorkomen van lokaal recidief werd gerelateerd aan de resectie marge, de aanwezigheid van ongunstige groeikenmerken (PG, VG, IG) en de gekozen aanvullende benadering (follow-up, re-resectie of postoperatieve radiotherapie (PORT)).
3. Follow up patiënten met een VM en follow-up patiënten met een KM (≥3mm <5mm) werden vergeleken.
4. De 3 jaar algemene overleving en ziekte specifieke overleving werd bepaald in relatie tot de resectie marge.

In totaal werden 200 patiënten met een stadium I-II OPCC van de tong, mondbodem of wang geïncludeerd.

- Negen van de 200 patiënten (4.5%) ontwikkelden een lokaal recidief.
- Van de 200 patiënten had 11% een PM, 63% een KM en 26% een VM.
-Eén recidief werd gevonden in de re-resectie groep, 5 in de PORT groep en 3 in de follow-up groep.
-Door de kleine aantallen kon het optreden van een lokaal recidief kon niet worden gerelateerd aan de resectie marge of ongunstige histologische groeikenmerken. Om dezelfde reden kon geen voorkeur voor aanvullende therapie worden bepaald.
-Vergelijking tussen patiënten met een VM en patiënten met een KM ≥3mm en ≤2 ongunstige groeikenmerken in de follow-up groep laat geen significant verschil zien in het optreden van recidief en de algemene en ziekte specifieke overleving.
-Er werd geen significant verschil gezien in algemene en ziekte specifieke overleving bij patiënten met een VM, KM of PM.

Conclusies hoofdstuk 5

- Met 4.5% is de kans op lokaal recidief klein ongeacht de resectie marge.

-Op basis van deze studie is er geen bewijs voor één aanvullende lokale therapie boven een andere.

-Wat het optreden van lokaal recidief betreft kon er geen bewijs worden gevonden voor aanvullende behandeling van T1-2 tumoren verwijderd met een marge van ≥3mm en ≤2 ongunstige groeikenmerken.

-Gezien de bijwerkingen in deze omstandigheden is het incorrect om aanvullende therapieën als re-resectie of PORT toe te passen bij vrije marges ≥3mm.

De hals

De aanwezigheid van halsklier metastasen bepaald voor een belangrijk deel de prognose van patiënten met een OPCC. Met onze huidige primaire staging technieken (Echo hals in combinatie met CT en/of MRI) missen we tussen de 20 en 40% van de halsklier metastasen. In **hoofdstuk 6** werden twee behandelstrategieën geëvalueerd. De selectieve nekdissectie level I II III (SND) en het nauwkeurig opvolgen van de hals (NOH). In geval van een SND is er sprake van een invasieve therapie met de mogelijke morbiditeiten. Indien gekozen wordt voor het NOH bestaat er een kans dat er reeds occulte metastasen aanwezig zijn en pas later ontdekt worden. Om inzicht te krijgen in de consequenties van de verschillende benaderingen werden de volgende onderwerpen bekeken.

1. De distributie van occulte metastasen over de verschillende behandelgroepen.
2. Het voorkomen van extra capsulaire groei bij SND patiënten en NOH patiënten met occulte metastasen.
3. Het voorkomen van ongunstige histologische parameters bij patiënten met metastasen (N+) en zonder metastasen (N-) in de NOH groep.
4. Het verschil in 3 jaar algemene overleving en ziekte specifieke overleving tussen de verschillende groepen.

In totaal werden 193 patiënten met een stadium I-II OPCC van de tong, mondbodem of wang geïncludeerd.

Bij patiënten met een geschatte tumordiameter <15mm en een infiltratiediepte <5mm werd alleen de primaire tumor verwijderd en de hals nauwkeurig opgevolgd. Bij de overige patiënten werd naast de tumorresectie een SND level I II III uitgevoerd.

-Van de totaal 193 patiënten bleken er 45 (23%) N+.
-Van de 123 SND patiënten bleken er 36 (29%) N+. Van de 70 patiënten in de NOH groep bleken 9 (13%) N+.
-Tenminste 4% van de patiënten had extra capsulaire groei in de SND-N+ groep.
-Tenminste 7% van de patiënten had extra capsulaire groei in de NOH-N+ groep.
-N+ Patiënten in de NOH groep hadden een significant grotere tumor infiltratie diepte in vergelijking met N- patiënten in deze groep. Ten opzichte van de overige ongunstige histologische kenmerken werden geen significante verschillen waargenomen.
-Patiënten in de SND groep en de NOH groep lieten een vergelijkbare algemene en ziekte specifieke overleving zien met respectievelijk 90% versus 86% (p=0.54).
-Patiënten in de SND-N+ groep hadden een significant betere ziekte specifieke overleving in vergelijking met patiënten in de NOH-N+ groep, 82% versus 56% (p=0.02). Er werd geen verschil gezien in algemene overleving tussen deze twee groepen.

Conclusies hoofdstuk 6

-Het beleid om tumoren met een geschatte diameter <15mm en infiltratie diepte <5mm voor wat betreft de hals op te volgen reduceert de a priori kans op een occulte metastase van 23% naar 13% bij patiënten met een stadium I-II OPCC van de tong, mondbodem of wang.

-Ondanks primaire staging en zorgvuldige selectie blijkt toch 13% van de patiënten in de NOH groep een occulte metastase te hebben en “onder” behandeld te worden.

-N+ Patiënten in de NOH groep bleken een significant grotere infiltratie diepte te hebben. Derhalve werd een SND geadviseerd bij een infiltratie diepte die groter blijkt te zijn dan 4mm.

-Strikt en nauwkeurig opvolgen is essentieel aangezien N+ patiënten in de NOH groep meer extra capsulaire groei toonden met een slechtere ziekte specifieke overleving in vergelijking met N+ patiënten in de SND groep.

Prognose

Behandelaars hebben een breed pallet aan behandelopties voor patiënten met een OPCC. Patiënten worden echter ouder, en de paternalistische patiënt dokter verhouding is langzaam aan het verdwijnen. Dit creëert spanning tussen de meest effectieve oncologische therapie, en de meest wenselijke therapie, aangaande leeftijd, co-morbiditeit en wensen van de patiënt. In **hoofdstuk 7** staat prognose centraal. Het doel van deze studie was om een predictie model te ontwikkelen met een nomogram om accuraat de 5 jaar postoperatieve overleving te kunnen bepalen om de behandelaar en patiënt te ondersteunen in het gezamenlijk besluit welke therapie de meest passende is.
475 opeenvolgende chirurgisch behandelde OPCC patiënten tussen 2003 en 2011 werden retrospectief geanalyseerd. Factoren geassocieerd met algemene overleving werden geïdentificeerd en ingevoegd in een predictie model en nomogram genoemd “oral oncoprognostic”.
De sterkste factoren gerelateerd aan algemene overleving waren leeftijd, synchrone primaire tumor, ASA classificatie, primaire tumor locatie, pathologisch T stadium, N stadium en de aanwezigheid van extra capsulaire groei.

Conclusies hoofdstuk 7
Oral oncoprognostic is een bruikbaar hulpmiddel om de algemene overleving te bepalen van post chirurgische patiënten. Het nomogram kan helpen bij patiënt begeleiding en individuele behandelplanning. Aanpassing aan de TNM 8 en externe validatie is echter noodzakelijk.

11

CHAPTER ELEVEN

Appendices

List of abbreviations

BI	Bony invasion
CM	Close Margin
CT	Computer Tomography
DSS	Disease Specific Survival
ECS	Extra Capsular Spread
FM	Free Margin
FNAC	Fine Needle Aspiration Cytology
G+	Positive Gain
G-	Negative Gain
IG	Infiltrative Growth
IOV	Inter Observer Variation
MRI	Magnetic Resonance Imaging
N+	Patients with nodal metastasis
N-	Patients without nodal metastasis
NPV	Negative Predictive Value
OS	Overall Survival
OSCC	Oral Squamous Cell Carcinoma
PG	Perineural Growth
PM	Positive Margin
PORT	Post Operative Radiation Therapy
PPV	Positive Predictive Value
RR	Re Resection
SNB	Sentinel Node Biopsy
SND	Selective Neck Dissection
US	Ultra Sound
VG	Vascular invasive Growth
WW	Watchful Waiting

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Curriculum Vitae

Eric Alexander Dik werd geboren op 9 september 1977 te Nieuwegein. In 1996 behaalde hij zijn vwo-diploma aan het st Gregorius college te Utrecht. Aansluitend is hij ingeloot voor de studie tandheelkunde, om in 2001 zijn tandarts examen aan het ACTA te Amsterdam te behalen. Om ervaring op te doen in het vak heeft hij vervolgens een jaar als tandarts gewerkt in een groepspraktijk in de omgeving Leiden, Voorburg en Den Haag. Na dat jaar is hij in 2002 begonnen aan de studie geneeskunde in Nijmegen, om in 2006 zijn artsexamen te behalen. Tijdens de studie geneeskunde is hij part time blijven werken als tandarts in een groepspraktijk in Lichtenvoorde. Na het artsexamen is hij in 2006 begonnen aan de specialisatie tot mond-, kaak- en aangezichtschirurg onder prof. dr. R. Koole aan het Universitair Medisch Centrum Utrecht. Na afronden van zijn specialisatie in 2010 kon hij direct aansluitend het fellowship hoofd hals oncologie doorlopen onder dr. R.J.J. van Es en prof. dr. A.J.W.P. Rosenberg eveneens in het UMCU. Na afronden van dit fellowship in 2012 volgde een korte waarneming in het Rijnstate Ziekenhuis in Arnhem waar hij samenwerkte met collegae dr. J.J.A. Brouns en dr. Th.J.M. Hoppenreijs in het hoofd hals oncologisch team ter plaatse. In dezelfde periode werd gestart met het promotieonderzoek aan het UMCU. Van 2013 tot 2018 heeft hij gewerkt als staflid MKA-chirurg, hoofd hals oncoloog aan de afdeling MKA-chirurgie van het Maastricht Universitair Medisch Centrum onder prof. dr. P.A.W. Kessler. Tijdens deze periode was hij van 2015 tot 2018 voorzitter van de hoofd hals werkgroep van het MUMC. Vanaf februari 2018 tot heden is hij werkzaam als staflid MKA-chirurg, hoofd hals oncoloog in het Radboud Universitair Medisch Centrum onder prof. dr. S.J. Bergé en prof dr. M.A.W. Merkx.