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Evaluation of neck dissection management in head and neck carcinomas

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Abbreviations

A.	artery (lat. arteria)
ALT	anterolateral thigh flap
c	TNM classification prefix modifier, i. e., status validated by clinical diagnostics (according to TNM classification, e.g., cN0, cMx)
cN0	clinically negative neck (no suspicious lymph nodes in the preoperative staging)
CT	computed tomography scan
CTx	chemotherapy treatment
DGMKG	The German Society for Oral and Maxillofacial Surgery (Deutsche Gesellschaft für Mund-Kiefer- und Gesichtschirurgie)
END	elective neck dissection
ENT	ear, nose, and throat practice
erND	extended radical neck dissection
HNSCC	head and neck squamous cell carcinoma
IJV	internal jugular vein (lat. vena jugularis interna)
LMU	Ludwigs-Maximilians University Munich (Ludwigs-Maximilians-Universität München)
M	metastasis status (according to TNM classification, see Table 12)
M.	muscle (lat. musculus)
MRI	magnetic resonance imaging
mrND	modified radical neck dissection
mVLF	myocutaneous vastus lateralis flap
N	nodal status (according to TNM classification, see Table 11)
N.	nerve (lat. nervus)
N0, N+/-	TNM nodal status (e.g., cN0, pN+, pN0, cN0, cNx)
ND	neck dissection
OR	odds ratio

OSCC	oral squamous cell carcinoma
OTSCC	oral tongue squamous cell carcinoma
p	TNM classification prefix modifier, i. e., status validated by histopathologic examination (according to TNM classification, e.g., pN0, pT3)
RCTx	combined radio- and chemotherapy treatment
RFF	radial forearm free flap
RKI	Robert Koch Institute
rND	radical neck dissection
RTx	radiotherapy treatment
RX	resection status (according to TNM classification, e.g., R0, R1; see Table 13)
SAN	spinal accessory nerve (cranial nerve XI, lat. nervus accessorius)
SCC	squamous cell carcinoma
SCM	sternocleidomastoid muscle (lat. musculus sternocleidomastoideus)
SLNB	sentinel lymph node biopsy
sND	selective neck dissection
sND	selective neck dissection
SPSS	Statistical Package of the Social Sciences (IBM SPSS, Inc, Chicago, IL)
T	tumor status (according to TNM classification, e.g., T1, T2; see Table 10)
TNM	International classification of Malignant Tumors [Brierley 2016, Sobin 2010]
TUM	Technical University Munich (Technische Universität München)
UICC	International Union Against Cancer
V.	vein (lat. vena)
WHO	World Health Organization
x	no statement possible (according to TNM classification, e.g., cMx)

1. Introduction

1.1. Head and neck cancer

The term head and neck cancer commonly summarizes a group of various malignant tumors originating from this anatomic region. Most of these tumors emerge from the local squamous cells making up the moist mucosal tissue of the head and neck. Because most of these tumors are of a biologically similar origin, they are often summarized as head and neck squamous cell carcinomas (HNSCC). This group usually describes malignant carcinomas of the lip, the oral and nasal cavities, the paranasal sinuses, the pharynx, the larynx, and the salivary glands [National Cancer Institute 2013]. The composition of the various tumor groups and subgroups is illustrated in **Figure 1**. The treatment of this heterogeneous group is divided between several different surgical disciplines: most commonly, between oral and maxillofacial surgeons, ear, nose, and throat surgeons, and neurosurgeons. The work in this thesis focuses on two important sub entities of the HNSCC group, namely on oral squamous cell carcinomas (OSCC) and on malignant tumors of the salivary glands. The basis of treatment for these forms of malignant disease is the surgical resection of the primary tumor, followed by neck dissection (ND) treatment and reconstruction of the primary tumor defect. The removal of potentially infiltrated malignant lymph nodes by neck dissection is a key to the oncologic treatment for the various entities of head and neck cancer. For most forms of head and neck cancer, the indications concerning the performance of ND treatment, i.e., whether and to what extent, are largely undisputed. However, cases of disease exist for which this decision is more strongly based on eminence than on evidence. Therefore, the work of this thesis also focuses on elective neck dissection (END) treatment and its indications in the treatment of head and neck cancer, namely for malignant tumors of the salivary glands and of the oral tongue. These two tumor entities will thus be presented in more detail in the following paragraphs. An illustrated overview of the research area covered by this work is given by **Figure 1**. All of the research described in this thesis has been published previously in two research articles in peer-reviewed international journals for oral and maxillofacial surgery by the author of this work. As the two articles represent the foundation of the work in this thesis, they will be presented in greater detail in the main chapters.

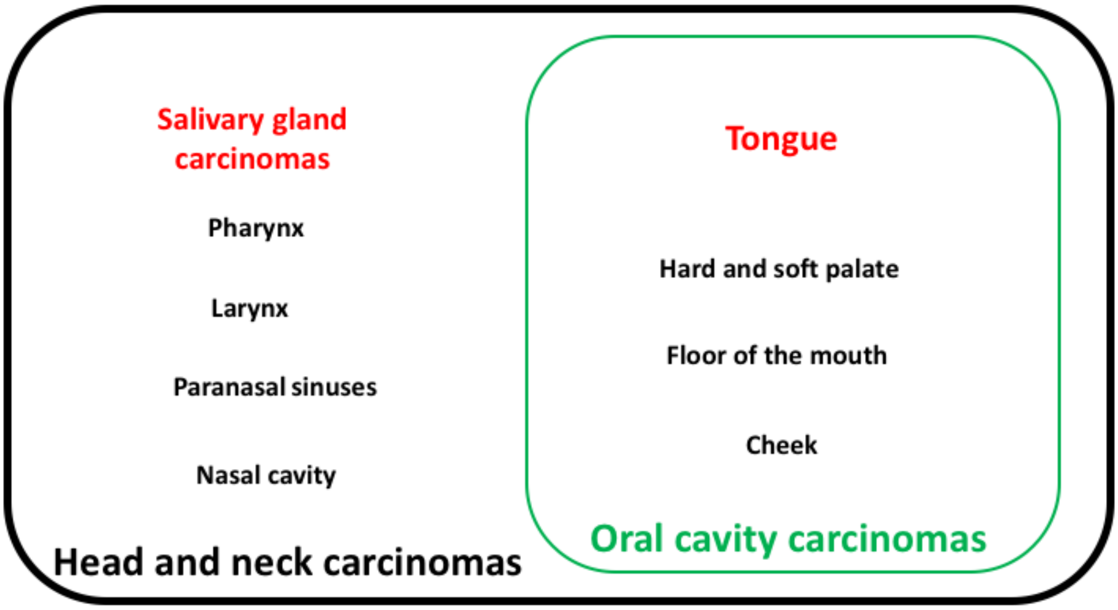

Figure 1: *Overview of the various subgroups of head and neck carcinomas.*

The entities focused on in this thesis are highlighted in red font.

1.1.1. Epidemiology

Over 90% of tumors of the head and neck region are squamous cell carcinomas. The remaining fraction is largely made up by adenocarcinomas, which are usually located in the salivary glands [Robert Koch Institut 2015]. Concerning malignant tumors of the pharynx and oral cavity in general, male patients are more often and also much earlier affected than are female patients. The mean age at disease is 62 years for men and 66 years for women. In German males, malignant tumors of the oral cavity and the pharyngeal region are the seventh most common tumors, with 9290 new cases in the year 2012, leading to an infection rate of 17.9. The absolute five-year-survival rates of 2011/2012 were 43% in male and 55% in female patients, whereas the relative five-year-survival rates were 48% in male and 61% in female patients. In view of longer periods of infection, the absolute ten-year-survival rate was 29% male and 40% for female patients, and the relative ten-year-survival was 36% for male and 50% for female patients [Robert Koch Institut 2015]. These rates also reflect the differences concerning patient gender in view of head and neck carcinomas; a concise overview of the mentioned values for the German population during years 2011/2012 is illustrated in **Table 1**.

Epidemiology of oral cavity and pharynx carcinomas for Germany, 2012

		Male	Female
New infections		9290	3650
Incidence rate[1]		23.64	8.87
Standardized incidence rate[1,2]		17.9	6.0
Mean age at disease onset[3]		62	66
Deaths		4090	1.303
Death rate[1]		10.41	3.17
Standardized death rate[1,2]		7.7	1.9
Five-year prevalence		28700	12400
Five-year-survival[4]	absolute	43	55
	relative	48	61
Ten-year-survival[4]	absolute	29	40
	relative	36	50

[1] per 100,000 people [2] age-standardized after old European population [3] median [4] in percent
Table information adapted from [Robert Koch Institut 2015].

Table 1: *Epidemiological key facts for carcinomas of the oral cavity and pharynx in Germany*

Salivary gland carcinomas

The clear majority of salivary gland tumors are benign pleomorphic adenomas that can be treated effectively by conservative salivary gland surgery [Bell 2005]. Malignant carcinomas make up a proportion of about 5% of all head and neck tumors [Bell 2005], representing 2.5–3.0 per 100,000 of all tumors per year [Andry 2012]. For Caucasian populations, studies have reported incidence rates of 1.1 per 100,000 per year [Bjorndal 2011, 2012]. Salivary gland carcinomas often demonstrate an unpredictable clinical behavior and course of development, e.g., high rates of locoregional failure and distant metastasis, which can all occur even after a long time following primary diagnosis. Survival rates for these kinds of tumors are also poor; the reported 5-year survival is 37% for high-grade tumors and about 90% for lower grades [Bell 2005].

Carcinomas of the oral tongue

In contrast to the vast variety of different tumor entities regarding the salivary glands, the situation for tumors of the oral tongue is far more clear. As shown by histopathology, the clear majority of the tumors of the oral tongue, with an amount of over 95% of all lingual malignancies, are squamous cell carcinomas (SCC) [Kari 1997, Moore 2000, Muir 1995, Ramirez-Amador 1995]. The tongue itself is also the most frequent location of oral cancer. For oral tongue squamous cell carcinoma (OTSCC), the amount of variation for male incidence per year rates is extremely large, depending on the local region and ethnicity. Rates from 9.4 in India to 1.1 in the UK have been reported in various studies. OTSCC is a disease that generally affects more men than women; the highest incidence rates are in the sixth to the eighth decades of life, whereas it rarely occurs below the age of 20 years [Moore 2000, Prince 1999]. The reported survival rates are relatively similar to the more general rates concerning oral cancer. The observed five-year survival is 65% overall (82% for disease stages I and II, 49% for stages III and IV) [Franceschi 1993].

1.1.2. Pathology of head and neck carcinomas

The two important forms of head and neck malignancies discussed by this work will be presented in the following paragraphs.

The OSCC

Carcinomas of the oral cavity are, as already mentioned, squamous cell carcinomas in 95% of cases [Muir 1995]. The SCC is a malignant epithelial tumor that shows evidence of squamous differentiation. It originates from the surface squamous epithelium or from ciliated respiratory epithelium that has undergone squamous metaplasia [Gale 2006b]. The malignant squamous differentiation is defined by the formation of intercellular bridges and/or keratinization, with keratin pearl formation. The macroscopic appearance of SCCs can be variable, which means that they can show (1) flat lesions with a well-defined raised edge, (2) polypoid, exophytic, or papillary lesions, or (3) endophytic infiltrative lesions. Ulcerations are a frequent feature on the tumor’s surface. This important fact is illustrated in **Figure 2**, which shows photographic images of various OSCC patients. The microscopic appearance of SCCs is characterized by an invasive growth pattern and squamous differentiation. The invasive growth pattern is characterized by the interruption of the basement membrane and the growth of islands, cords, or single/dyscohesive tumor cells in the subepithelial stroma. In further advanced malignant tumors, an invasion of the deeper structures, e.g., muscle, cartilage, and bone is common. Perineural or invasion of lymphatic and blood vessels can be observed and are thus reliable evidence of cancer invasiveness [Gale 2006b].

Figure 2: *Various images of OSCC, illustrating the large variety of its macroscopic appearance.* Photographic images are the property of Kesting, M. R.

Salivary gland malignancies

Salivary gland tumors are a highly heterogeneous group, featuring many different benign and malignant variants. The therapeutic management of salivary gland cancers is therefore highly challenging because of their rarity in conjunction with their large variety of histologic types and grades [Dias 2007]. The World Health Organization (WHO) recognizes 24 different malignant entities. This extensive number of different tumors is given in **Table 2** from the WHO [Barnes 2005].

WHO histological classification of tumors of the salivary glands

Malignant epithelial tumors
- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Clear cell carcinoma, not otherwise specified
- Basal cell adenocarcinoma
- Sebaceous carcinoma
- Sebaceous lymphadenocarcinoma
- Cystadenocarcinoma
- Low-grade cribriform cystadenocarcinoma
- Mucinous adenocarcinoma
- Oncocytic carcinoma
- Salivary duct carcinoma
- Adenocarcinoma, not otherwise specified
- Myoepithelial carcinoma
- Carcinoma ex pleomorphic adenoma
- Carcinosarcoma
- Metastasizing pleomorphic adenoma
- Squamous cell carcinoma
- Small cell carcinoma
- Large cell carcinoma
- Lymphoepithelial carcinoma
- Sialoblastoma

Benign epithelial tumors
- Pleomorphic adenoma
- Myoepithelioma
- Basal cell adenoma
- Warthin tumor
- Oncocytoma
- Canalicular adenoma
- Sebaceous adenoma
- Lymphadenoma
  - Sebaceous
  - Non-sebaceous
- Ductal papillomas
  - Inverted ductal papilloma
  - Intraductal papilloma
  - Sialadenoma papilliferum
- Cystadenoma

Soft tissue tumors
- Hemangioma

Haematolymphoid tumors
- Hodgkin lymphoma
- Diffuse large B-cell lymphoma
- Extranodal marginal zone B-cell lymphoma

Secondary tumors

Table information adapted according to [Barnes 2005].

Table 2: *The various tumors of the salivary glands, as recognized by the WHO*

Carcinomas of the salivary glands can be divided into three major categories according to their histopathologic origin of development. These specific groups are further listed in **Table 3**.

The three major categories of salivary gland malignancies

• Tumors of epithelial origin	E.g., mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, malignant mixed tumor, squamous cell carcinoma, salivary duct carcinoma, etc.
• Tumors of non-epithelial origin	E.g., sarcomas and lymphomas
• Secondary tumors	

Table information adapted from [Dias 2007].

Table 3: *The three major histopathologic groups of salivary gland malignancies*

With regard to the overall number of salivary gland tumors, malignant neoplasms only make up less than a quarter. The clinically most encountered subtypes of this malignant fraction are the adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and acinic cell carcinoma [Bell 2005, Bjorndal 2011, 2012, Malata 1997, Nobis 2014, Spiro 1978, Witten 1990].

1.1.3. Risk factors

A wide variety of different risk factors contributes to oral cancer development, as presented in **Table 4**. The carcinomas of the head and neck region all generally have the same risk factors in common, because about 95% of them are OTSCC. As for most malignant tumors, advanced age is one of the common risks for tumor development [Robert Koch Institut 2015], but these specific carcinomas are also highly associated with risk factors such as chronic smoking or alcohol consumption. Studies investigating risk factors have provided odds ratios (OR) of 19.8 for smokers compared with patients never exposed to smoking and 5.9 for alcohol consumption (>55 drinks/week) [Wolff 2012b]. A combined exposure of both tobacco and alcohol leads to a multiplication effect, with an OR of 177 [Talamini 2002]. The harming effect of alcohol on the oral mucosa is believed additionally to allow the cancerogenous substances of the inhaled smoke to penetrate the affected skin more efficiently [Squier 1986]. These studies illustrate the strong influence of alcohol and tobacco on OSCC tumor etiology. An elimination of the two lifestyle factors of alcohol and tobacco is estimated to be able to prevent up to 75% of OSCC [Scully 2011]. Studies have shown that a cessation of smoking alone might contribute to the risk reduction of OSCC development. A reduction of 35% might be achieved within 1-4 years and a reduction of 80% within 20 years, ultimately reaching the same level as that of individuals who have never smoked [Marron 2010]. An additional identified risk factor is poor oral hygiene or consistent mechanical irritation of the oral mucosa. For this reason, regular dental check-ups are effective in decreasing the risk of OSCC development [Rosenquist 2005b].

Overview of risk factors for OSCC development	
Lifestyle factors	• Alcohol • Tobacco • Paan *(Betel quid/Areca nut, mixed with or without tobacco)* • Maté *(South American tea-like beverage)* • Perserved or salted food • Shammah *(traditional Arabian smokeless tobacco habit)*
Infections	• Bacterial infections *(e.g. poor oral hygiene, dental plaque)* • Candidiasis • Human papillomavirus *(especially HPV-16 and HPV-18)* • Herpes virus • Epstein-Barr virus
Genetics	E.g., loss of protective genetic mechanisms, such as genes for the xenobiotic metabolizing liver enzymes (XME), DNA repair genes, genes for the repair of damaged growth control or the controlled death of cancerous cells (TSGs), and genes related to immune protection
Poor social and economic status	E.g., deprivation through low educational attainment, low occupational social class, and low income. These associations are observed particularly strong for men
Immune deficiencies	E.g., diabetes, cytostatic medication
Environment	Ionizing radiation *(from natural or therapeutic sources)*
Oral lesions	E.g., pressure lesions caused by a prosthesis

Table information adapted from [Bagan 2008, Balaram 2002, Conway 2008, Marur 2010, National Cancer Institute 2013, Rosenquist 2005a, Rosenquist 2005b, Scully 2011, Walker 2003, Wolff 2012b].

Table 4: *Overview of the large variety of different risk factors for oral cancer tumor development*

1.1.4. Diagnosis and preoperative staging of head and neck cancer

Patients can present with a large variety of different clinical symptoms. In general, the German guideline for the treatment of oral cancer recommends the presentation of a patient with any mucosal lesions of unknown origin and of more than two weeks' duration to be immediately sent to a specialized treatment facility. An overview of possible symptoms is given in **Table 5**.

Common oral cancer symptoms

- White or red spots anywhere on the oral mucosa
- A mucosal defect or ulceration
- Swelling anywhere in the oral cavity
- Loosening of one or more teeth for no known reason, not connected with periodontal disease
- Persistent foreign body sensation, particularly when unilateral
- Pain
- Difficulty or pain in swallowing
- Speech difficulties
- Reduced mobility of the tongue
- Numbness of the tongue, teeth, or lips
- Bleeding of unknown origin
- Neck swelling
- Fetor ex ore
- Altered dental occlusion

Table adapted from the German guideline for oral cancer treatment [Wolff 2012b].

Table 5: *An overview of the possible symptoms of oral cavity cancer*

After presentation with one of the illustrated symptoms, patients should be thoroughly examined. The clinical examination should feature a thorough oral and extraoral investigation.

1.1.5. Current treatment strategies

The treatment of head and neck carcinomas has the goal of removing all tumor tissue and of lowering the probability of later tumor recurrence as much as possible. All treatment procedures have to pay great respect to the patient’s quality of life, and therefore, future esthetic and functional disabilities caused by medical procedures must be minimized. All strategies should be evidence-based and in accordance with international research consent. Nowadays, the treatment of head and neck malignancies is carried out in specialized treatment centers with high expertise. Treatment is performed by an interdisciplinary team of all involved medical disciplines, e.g., oral maxillofacial surgeons, ENT surgeons, radiotherapists, radiologists, pathologists, and oncologists. In oncologic centers, the specialists form an interdisciplinary board to optimize each patient’s individual treatment procedure.

As for most malignant tumors, the selected treatment depends on the patient’s prognosis, giving the options of curative and palliative treatment. The curative treatment features the removal of the tumor lesion, either by surgery alone, by primary radiotherapy alone, or by combination of both [Fein 1994, Glenny 2010, Murthy 2010, Olmi 1988, Wolff 2012a].

The palliative treatment commonly features chemotherapy and radiotherapy as additional measures. The palliative goal is the improvement of the remaining quality of live by trying to achieve tumor control and the minimization of symptoms for as long as possible.

The standard curative treatment procedure according to the German guideline for the treatment of oral malignancies [Wolff 2012a] will be explained in more detail in the following paragraphs. An overview of the treatment algorithm used clinically to address oral malignancies in accordance with the above-mentioned guideline is given in the following **Figure 3**.

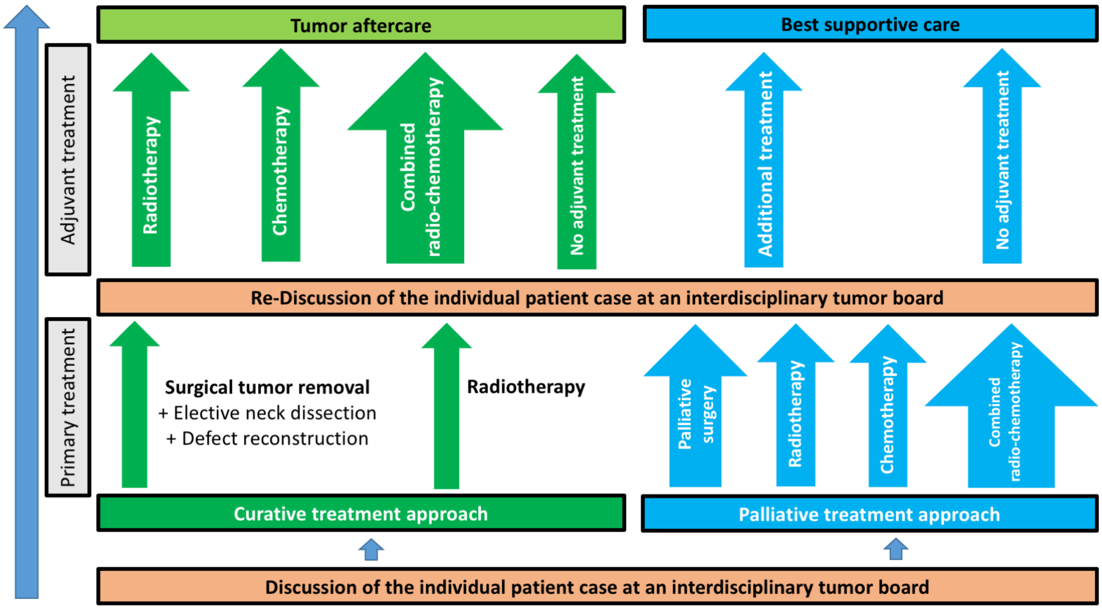

Figure 3: *Clinical treatment algorithm for malignancies of the oral cavity*

Primary tumor resection

One of the most important factors in ablative tumor surgery is the achievement of clear resection margins. In the case of OSCC, a safety margin of 5 mm of healthy uninvolved tissue around the primary tumor is viewed as an R0 resection status. A resection distance of less than 1 mm is considered as a positive margin, whereas 1 to 3 mm is considered as a narrow margin [Loree 1990, McMahon 2003, Wolff 2012b]. This logically leads to a relatively large volume of tissue having to be resected, which can be extremely complicated in the detailed and confined anatomic conditions of the head and neck region. Ideal possibilities for the resection of all the various tumor types in their whole circumference are therefore rarely present [Kesting 2015]. In consequence, a huge variety of different surgical techniques has been developed over the years to grant access for tumor resection, and because of this large amount, only a few key techniques will be mentioned in the following. Neoplasms of the pterygomandibular region, the base of the tongue, and the oropharynx can be approached by different variations of the lip-split mandibulotomy access, whereas extended neoplasms of the maxilla, the maxillary sinus, and neighboring tissues can be approached via the so-called Weber-Fergusson-Dieffenbach method. More advanced malignancies of the maxilla, central midface, or nasal cavity can be addressed by midfacial degloving, and tumors of the maxilla infiltrating anterior and middle parts of the maxillary sinus can be addressed by the Le-Fort-I-Osteotomy approach [Kesting 2015].

Elective neck dissection

The primary tumor resection is usually followed by an elective neck dissection with various forms of extension according to the patient’s individual tumor risk profile. Because of the high relevance of END treatment for the clinical therapy of head and neck cancer, a section (chapter 1.2) of this thesis is devoted to it.

Defect reconstruction

The removal of the primary tumor lesion and its healthy surrounding tissue in order to achieve sufficient safety margins leads to large defect areas. In the head and neck region with their dense anatomical structures, tumor defects heavily influence function and esthetics. Therefore, the subsequent reconstruction of functionality and esthetics after tumor removal is a necessary and complicated goal. The principle for sensible defect reconstruction follows the so-called reconstructive ladder [Mardini 2005], as illustrated in **Figure 4**. Special attention should be given to critical factors for sufficient surgical wound management, e.g., second-intention healing, primary wound closure, skin grafting, and reconstruction with local or distant free flaps [Riedel 2005]. Depending on the patient’s status and defect size, the decision for optimal defect closure treatment is made accordingly.

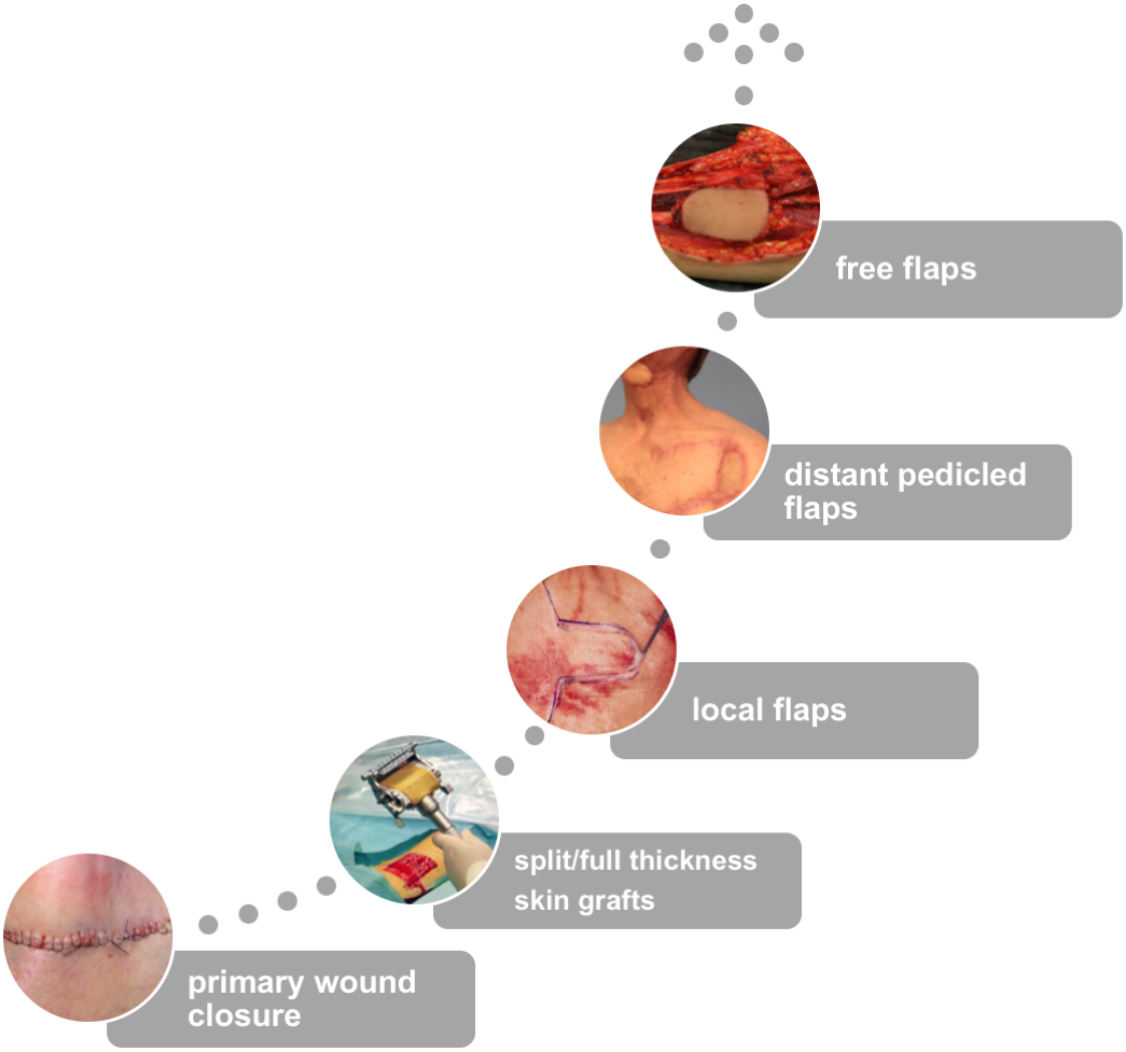

Figure 4: *Illustration of the "reconstructive ladder" principle for defect coverage*

Photographic images are the property of Kesting, M. R.

Small defects without heavy loss of tissue can be closed primarily by appropriate suture techniques. Larger defects need split or full thickness skin grafts from appropriate donor sites, e.g., the inguinal region. Depending on the location and size of tissue loss, larger and deeper defects can be closed by local flap techniques, which can be escalated up to local pedicled flaps. The final tools for defect closure are the microvascular free flap transplants. These flaps have become very popular for wound closure, because of their almost endless range of sizes, donor sites, and pedicle vessels. The large number of different microvascular transplants offers the possibility of finding the optimal transplant for each specific patient, according to their specific advantages and disadvantages. The strengths and weaknesses of the three most commonly used flaps for facial defect coverage are listed in **Table 6**.

Overview of the most commonly used microvascular flaps

Micro-vascular transplant	**Flap pedicle**	**Available flap tissue**	**Some flap advantages and disadvantages**
Radial forearm flap (RFF)	Radial artery	Myo-cutaneous	+ In comparison, easier process of flap raising + Widely used “workhorse” flap + Good modeling possibilities for defect coverage + Variability in flap perfusion + High vessel caliber and long vascular pedicle + Easy anastomosis + Possibility to include cephalic vein - Flap raising is only possible if superficial and deep palmar arch are connected (necessity of preoperative Allen-Test to validate hand perfusion after artery loss) - Donor-site defect coverage necessary for tendon protection (e.g., via full- or split-skin-thickness grafts) - Exponent donor-site defect - Reduced strength, extension, and possible sensitivity reduction of the donor-site hand - Tendency of edema formation
Myocutaneous vastus lateralis flap (mVLF)	Descending branch of the lateral circumflex femoral artery	Myo-cutaneous	+ Possibility for the reconstruction of large defect sizes + Flexible variation of thickness and volume + Primary wound closure usually possible + Normally no significant or functional donor-site impairments - Variations in vascular anatomy (e.g., pedicle length) - Flap thickness can be disadvantageous for intraoral defect closure (flap thinning procedures sometimes necessary) - Substantial hair growth possible on the skin of the transplant
Fibula flap	Peroneal artery with periostal branches	(Osteo-) myo-cutaneous	+ Bony reconstruction of the mandible + Longest bone flap available + Good stability (high amount of cortical bone) + Similar quality of the thin and pliable skin paddle to that of the RFF + Good flexibility of the skin island + Long pedicle vessel of high caliber + Easy anastomosis + Immediate possibility of future dental rehabilitation via implant insertion + Generally low donor-site morbidity (e.g., instability of the ankle joint rather uncommon) - Limited skin island size - Low bone thickness - Primary donor-site wound closure often not possible because of tensions (full- or split-skin-thickness grafts needed) - High variability of cutaneous perforating vessels and thus unreliability in skin island supply - Common arteriosclerotic changes of the lower leg vessels

Table information adapted from [Wolff 2011].

Table 6: *Facts with regard to three important microvascular free flaps for defect coverage*

1.1.6. Postoperative care

The necessary postoperative care is decided for every patient individually by an additional presentation to an interdisciplinary board for head and neck oncology. The tumor board then decides on the further process of additional therapy and tumor follow-up with consideration of the latest histopathologic and clinical examinations. In general, the tumor aftercare features continuous clinical controls every 3-6 months and a computed tomography scan every year during the first five years. After an absence of tumor recurrence for this period, CT scans can be performed on a two-yearly basis from there on, but always in accordance with the patient’s risk for tumor development or recurrence.

1.2. Neck dissection

The term neck dissection is commonly used to describe the surgical removal of the lymph nodes of the head and neck, i.e., a lymphadenectomy. In the current treatment of head and neck malignancies, elective neck dissection is one of the key tools for addressing malignant tumors. The following sections present an overview of this important surgical procedure.

1.2.1. History

Surgeons in the nineteenth century were aware that the spread of oral cancer to the lymph nodes of the patient’s neck would lead to a poor prognosis. Prior to the beginning of the nineteenth century, almost no serious attempts were made in order to treat this metastatic lymph node spread. The view from cases that were reported and that mainly involved just the removal of single pathologic lymph nodes was that this treatment brought no benefit to the affected patients [Rinaldo 2008].

The first neck dissection is considered to be the one performed by a Polish surgeon from Warsaw, *Franciszek Jawdynski* (1851-1896). He performed a radical neck dissection on patients that had head and neck carcinomas and that were already showing signs of distant metastasis [Jawdynski 1888]. Probably as a result of Jawdynski publishing his report in the Polish language only, his work did not become widely known throughout the academic world of that time.
The first prophylactic or elective neck dissection, as this procedure is usually termed nowadays, was performed in 1885 by the British surgeon *Sir Henry Trentham Butlin* (1845–1912). He promoted removing the neck’s lymphatic tissue through a “Kocher

incision” and additionally suggested that this kind of treatment should be performed on a routine basis in the therapy of tongue cancer patients [Butlin 1885]. His idea can be seen as the first breakthrough in the development of an elective treatment strategy for addressing regional metastatic disease in head and neck cancer patients and, in consequence, made him one of the fathers of British head and neck surgery [Rinaldo 2008]. The first report that was based on a greater patient collective and that became more widely renown was published in 1906 by *George Washington Crile* (1864-1943) [Silver 2007]. He described the experiences that he made with a form of radical neck dissection based on 132 different treatment cases. The next step in the history of the evolution of this method was the principle of modified radical neck dissection. This was first reported in 1962 by the Argentinian surgeon *Osvaldo Suarez* (1912-1972) [Suarez 1962]. As most of his relevant publications were in the Spanish language, his achievements did not reach the larger research population. About five years later, the Italian surgeon *Ettore Bocca* (1914-2003) was responsible for promoting this technique by publishing, in the English language for the international audience, his experiences in Argentina [Bocca 1967]. The standard principle of selective neck dissection featured in these related studies was finally developed and published during the 1980s [Byers 1985] and has since become one of the essential columns of treatment for head and neck carcinomas.

1.2.2. Various forms and extensions

Surgical neck dissection treatment is usually divided into four different forms, some of which are used today, and others of which are only of historical relevance. These include the radical neck dissection (rND), the extended radical neck dissection (erND), the modified radical neck dissection (mrND), and several different forms of selective neck dissections (sND) [Robbins 2002]. The removal of all ipsilateral cervical lymph node groups (levels I to V) in combination with a removal of the SAN, internal jugular vein, and SCM is called radical neck dissection. The modified radical neck dissection differs from the radical method by the preservation of one or more non-lymphatic structures (e. g., SAN, internal jugular vein, or SCM). It is common practice specifically to name the preserved structures, e. g., a modified radical neck dissection with preservation of the SAN. The extended radical neck dissection refers to a radical neck dissection that features the additional removal of one or more extra lymph node groups, non-lymphatic structures, or both. These do not have to be included in the radical neck dissection. An example for additional non-lymphatic tissues that might be resected during extended radical neck dissection is the carotid artery, hypoglossal nerve, vagus nerve, or paraspinal muscles. A selective neck dissection refers to a neck dissection that is performed in accordance with the primary tumor staging [Robbins 2002]. This method is the standard procedure in cN0 OSCC patients [Wolff 2012a]. In these cases, the technique includes the removal of the ipsilateral lymph node levels I-III. An additional name, because of the anatomic location, is the supraomohyoid neck dissection. The fact that a ND is often used as a prophylactic form of treatment in patients with a clinically unsuspicious neck has established the term elective neck dissection for this procedure. The various forms of neck dissections are summarized in the following **Table 7**.

Overview of the different forms of neck dissection		
Type	**Extension of resection**	**Indication**
Radical neck dissection (rND)	Removal of the ipsilateral lymph node levels I-V, the SAN, internal jugular vein, and SCM	Mainly historic
Extended radical neck dissection (erND)	Removal of the same as in the radical neck dissection, but additional removal of one or more extra lymph node groups, non-lymphatic structures, or both	Mainly historic
Modified radical neck dissection (mrND)	Removal of the same as in the radical neck dissection, but instead preservation of one or more non-lymphatic structures (ie. g. SAN, internal jugular vein, or SCM)	cN+ patients
Selective neck dissection (sND)	Extension depending on the preoperative staging. Usually, the sparing of one or more lymph node levels (e. g., ipsilateral sND, levels I-III).	cN0 patients; method often used as prophylactic treatment, when it is then called elective neck dissection (END)

Table information adapted from [Robbins 2002, Robbins 1991].
Table 7: *The most important forms of neck dissection*

1.2.3. Classification system for lymph nodes of the head and neck

The system of classification that is internationally the most frequently used is the one originally published by Robbins in 1991 [Robbins 1991]. It was updated and modified in 2002 [Robbins 2002]. In this classification, the lymphatic tissue of the head and neck region are divided into levels and sublevels, as illustrated in **Figure 5** as taken from the corresponding publication [Robbins 2002].

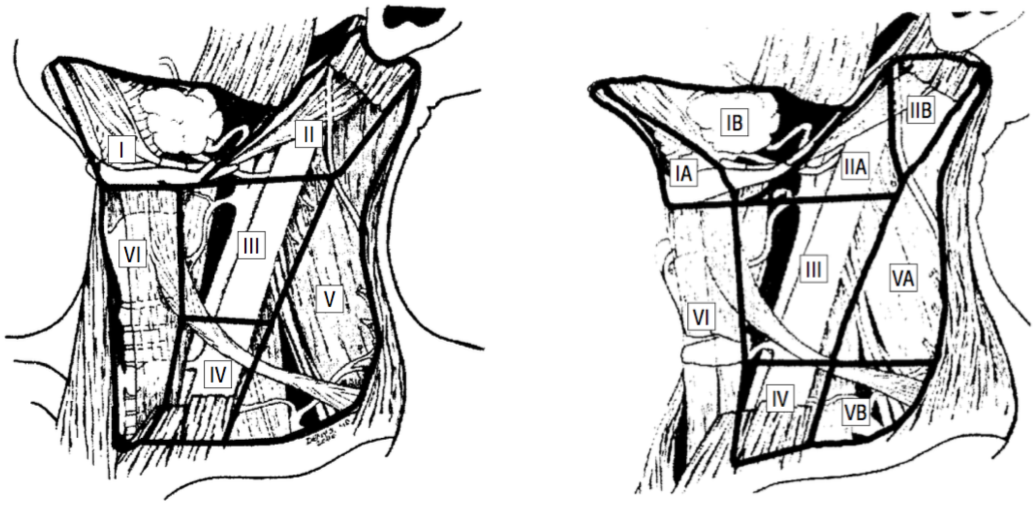

Figure 5: *Illustrations of the lymph node levels of the neck (left) and its division into sublevels (right).*

Illustrations are from the corresponding publication of [Robbins 2002].

With regard to the anatomic borders of the levels and sublevels of the neck, level I consists of the submental and submandibular nodes. The corresponding sublevels IA are in the submental triangle, and IB in the submandibular triangle. Level II consists of the upper jugular nodes and can also be divided into two sublevels. Sublevel IIA features the lymph nodes, which are located medial to the vertical plane defined by the spinal accessory nerve (SAN), and sublevel IIB in consequence features the lymph nodes that are located lateral to the vertical plane defined by the SAN. The middle jugular lymph nodes are in level III, and the lower jugular nodes in level IV. Level V consist of the lymph nodes of the posterior triangle group and can again be divided into two sublevels. Sublevel VA features the lymph nodes above the cricoid, and sublevel VB the lymph nodes beneath [Robbins 2002]. These definitions and anatomic borders as explained above can also be found below in **Table 8**.

Definition and anatomic description of the lymph nodes of the head and neck			
Level I	Submental and submandibular nodes	*Level IA* *Level IB*	Submental triangle Submandibular triangle
Level II	Upper jugular nodes	*Level IIA*	Lymph nodes located medial to the vertical plane defined by the SAN
		Level IIB	Lymph nodes located lateral to the vertical plane defined by the SAN
Level III	Middle jugular nodes		
Level IV	Lower jugular nodes		
Level V	Posterior triangle group	*Level VA* *Level VB*	Lymph nodes above the cricoid Lymph nodes beneath the cricoid

Definitions and anatomic descriptions based on the classification of [Robbins 2002].
Table information adapted from [Kesting 2015].
Table 8: *Definition and anatomic description of the cervical lymph nodes*

1.2.4. The TNM classification of malignant tumors

The TNM classification is an international system developed by the UICC (Union for International Cancer Control) to classify and stage various forms of malignant solid tumors [Brierley 2016, Sobin 2010]. These international guidelines for tumor classification are updated on a regular basis. The original research articles presented in this paper were based on the 7th edition of the TNM classification [Sobin 2010], which was the current one at the time that the research was carried out and the results were published. At the end of the year 2016, an updated 8th version was released by the UICC [Brierley 2016]; it came into effect on January 1st, 2017. To stay in accordance with the TNM classification used in the presented original research articles, the following section is still based on the 7th edition of the TNM classification. The differences and between these two editions are highlighted in **Table 9**.

The differences between the 7th and 8th edition of the TNM classification

	Clinical	**Pathological**
N1, N2a, N2b, N2c	Unchanged other than specify without extranodal extension	Unchanged other than specify without extranodal extension
N3a	Metastasis in a lymph node more than 6cm in greatest dimension without extranodal extension	Metastasis in a lymph node more than 6cm in greatest dimension without extranodal extension
N3b	Metastasis in a single or multiple lymph nodes with clinical extranodal extension (a clinical extra nodal extension is defined as the presence of skin involvement or soft tissue invasion with deep fixation/tethering to underlying muscle or adjacent structures or clinical signs of nerve involvement)	Metastasis in a lymph node more than 3cm in its greatest dimension with extranodal extension or multiple ipsilateral or any contralateral or bilateral node(s) with extranodal extension

Table information from an update presentation on the UICC website and from both TNM edition releases [Brierley 2016, Sobin 2010, Union for International Cancer Control (UICC) 2016].

Table 9: *Overview of the differences regarding cervical lymph nodes between the 7th and 8th edition of the TNM classification*

As mentioned above, the TNM classification is used to classify and stage malignant solid tumors. In order to do so, the system uses alphanumeric codes that are presented in depth by **Table 10**, **Table 11**, **Table 12**, and **Table 13**. The malignancies are categorized and assigned to the different tumor stages, according to specific classification parameters. The main parameters of this staging system are represented by the capital letters T, N, and M, which stand for tumor, nodes, and metastasis. The letter T gives information about the size or direct extent of the primary tumor (**Table 10**), the letter N about the degree of spread to regional lymph nodes (**Table 11**), and the letter M about the presence of distant metastasis (**Table 12**). The capital letter is advanced by a prefix modifier, which can be an indication of previous therapies or based on specific diagnostics (e.g., from histopathologic specimens or from clinical examination). After the capital letter follows a suffix to indicate the degree or extent of the parameter; this is usually specific to the described malignancy. This notation can be further edited via the addition of other various coding parameters giving, for example, further information about tumor grading or about the postoperative resection status. Some of the more frequently used additional parameters are listed in **Table 13**. To illustrate the explanations above, some examples will be given in the following. The code Tis, for example, is used to describe a carcinoma in situ, whereas the code T4 is the highest value of the T-stage category and is commonly used for a primary tumor that is already infiltrating neighboring organs. In combination with the prefix modifier, cT4 would mean that this diagnosis is based on clinical examinations and not from histopathologic examinations. The classification is of great importance for clinical cancer treatment, because tumor stage remains the most significant predictor of patient survival. The tumor's size itself and the presence of regional and/or distant metastases are themselves independent predictors of survival [Gale 2006a].

The tumor status

c	*Clinical status*	+	**T**	+	**X**	*No statement possible*
p	*Pathological status*				**is**	*Carcinoma in situ*
u	*Ultrasound*				**0**	*No evidence for primary tumor*
y	*Neoadjuvant therapy*				**1-4**	*Tumor advancement (entity specific)*
r	*Recurrence*					
a	*Autopsy*					

Table 10: *Composition of T-status in the TNM classification*

The nodal status

c	*Clinical status*	+	**N**	+	**X**	*No statement possible*
p	*Pathological status*				**0 / -**	*No evidence for primary tumor*
					+	*Positive lymph nodes*
					(sn)	*Sentinel lymph node*
					1-3	*Nodal advancement (entity specific)*

+ (X / X) *Amount of positive lymph nodes, e.g., pN1 (3/24)*

Table 11: *Composition of N-status in the TNM classification*

The metastasis status

c	*Clinical status*	+	**M**	+	**X**	*No statement possible*
p	*Pathological status*				**0**	*No evidence for primary tumor*
					1	*Distant metastasis*

+ (OSS) / (HEP) / etc. *Abbreviated location of distant metastasis, e.g., (BRA) for brain or (HEP) for liver*

Table 12: *Composition of M-status in the TNM classification*

Other TNM classification variables	
L0/1	Invasion into lymphatic vessels
V0/1	Invasion into veins
Pn0/1	Perineural invasion
R0/1	Resection status
G1-4	Tumor grading
C1-5	Factor of certainty for the last parameter

Table 13: *Overview of the other commonly found variables in the TNM classification*

The exact form of coding with the TNM system varies between different tumor entities. Individual TNM classifications exist for specific groups of malignant tumors, e.g., for gastric tumors, head and neck tumors, etc. The T-stage is, for example, often based on the size and anatomic infiltration of the primary lesion. An example of a specific T-stage coding is given in **Table 14** for tumors of the lip and oral cavity. The exact nodal TNM classification for these tumors is given in **Table 15,** and the metastasis stages in **Table 16**.

T-stages of the lip and oral cavity		
TX		Primary tumor cannot be assessed
Tis		Carcinoma in situ
T0		No evidence of primary tumor
T1		Tumor 2 cm or less in greatest dimension
T2		Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3		Tumor more than 4 cm in greatest dimension
T4a	Lip	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
	Oral cavity	Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b		Tumor invades masticator space, pterygoid plates, or skull base, or encases internal carotid artery

Table information adapted from [Barnes 2005, Wittekind 2015].
Table 14: *The specific T-stages for carcinomas of the lip and oral cavity*

N-stages of the lip and oral cavity		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
	N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2	**N2b**	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3		Metastasis in a lymph node more than 6 cm in greatest dimension
Cave: Midline nodes are considered ipsilateral nodes		

Table information adapted from [Barnes 2005, Wittekind 2015].
Table 15: *The specific N-stages for carcinomas of the lip and oral cavity*

M-stages of the lip and oral cavity	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table information adapted from [Barnes 2005, Wittekind 2015].
Table 16: *The specific M-stages for carcinomas of the lip and oral cavity*

A tumor that has been assessed with the TNM system can now be classified further into disease stages. These are also specific for each individual kind of tumor. The disease stages are usually numbered from I to IV and are a reflection of the clinical disease advancement. The distribution into disease stages is based on the patient's individual TNM classification. **Table 17** illustrates this procedure based on the example of lip and oral cavity carcinomas.

Disease stages for lip and oral cavity carcinomas				
Stage 0		Tis	N0	M0
Stage I		T1	N0	M0
Stage II		T2	N0	M0
Stage III		T1 / T2 T3	N1 N0 / N1	M0 M0
Stage IV	**A**	T1 / T2 / T3 T4a	N2 N0 / N1 / N2	M0 M0
	B	Any T T4b	N3 Any N	M0 M0
	C	Any T	Any N	M1

Table information adapted from [Barnes 2005, Wittekind 2015].
Table 17: *The specific disease stages for carcinomas of the lip and oral cavity*

1.2.5. Clinical neck dissection management

For oral malignancies in general, ipsilateral neck dissection from levels I to III is performed in all previously not operated malignancies (also called supraomohyoid neck dissection). Bilateral neck dissection from levels I to III is indicated when the intraoral malignancy extends over the midline. It is helpful to begin the neck dissection with the dissection of ipsilateral levels II and III. The clinical situs of a ND during surgical procedure is illustrated in **Figure 6** below.

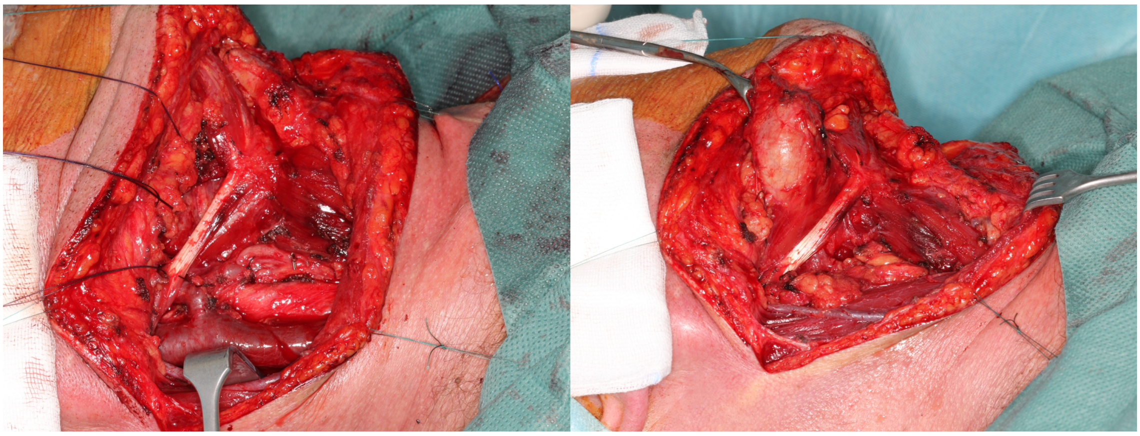

Figure 6: *Clinical situs during neck dissection surgery.*

Photographic images are the property of Kesting, M. R.

The acquired lymph nodes from this region can then be sent immediately for frozen-section histopathologic examination. The time waiting for the pathologist's results is used for the dissection of level I. If the intraoperative frozen sections give positive results, the neck dissection is extended to levels IV and V on the ipsilateral and levels I to III on the contralateral side of the neck. In cases of a clinically negative neck, the so-called cN0 neck, a functional neck dissection is performed. Hereby, strict attention should be paid to preserving the spinal accessory nerve (SAN), the sternocleidomastoid muscle (SCM), and the internal jugular vein (IJV). In positive necks, the anatomic structures mentioned previously should always be preserved, when clear resection margins to the lymph node metastases are possible. A modified radical neck dissection is performed if lymph node positive necks show clear adherence of lymph node metastases to one of the previous structures. The adhered structure (SAN, SCM, or IJV) now should be included in the dissection. The maximum extent of neck dissection treatment is the radical neck dissection. It is preformed when, in a neck with positive lymph nodes, all the three above-mentioned structures show adherence to metastasis. Notably, an en-bloc resection of the neck dissection specimen does not show any evidence-based clinical benefit. The presented strategy of splitting the neck dissection therefore not only saves time, but also facilitates the discussion at the postoperative tumor board, in which the most exact pinpointing of cervical metastasis location is required for effective adjuvant radiotherapy [Kesting 2015].

1.2.6. Indications and treatment value of elective neck dissection

In the preceding chapters, the importance of neck dissection treatment in head and neck carcinoma patients has been thoroughly highlighted. The key to successful surgical therapy also greatly depends on choosing the right indication for treatment. In cases of elective neck dissection, some of the cases are clearer than others. Some clinical situations still miss evidence-based treatment guidelines and are, to date, just based on subjective experiences made in the specific treatment center. In Germany, a common guideline for the treatment of OSCC has been published by *Wolff et al*. for the DGMKG [Wolff 2012a]. In the case of carcinomas of the oral floor, the S-3 German guideline suggests an ipsilateral neck dissection of levels I to III in all previously untreated malignancies. A bilateral neck dissection including the contralateral levels I to III is performed if the malignancy extends over the midline.

1.2.7. Disputed cases of neck dissection treatment

The German guideline and the international literature have much in common regarding the indication of END for intraoral carcinomas below the intercalary line. For many other entities of malignant head and neck tumors with their specific locations and extensions, the indications are much more disputed. Two widely viewed examples are the cases regarding cN0 salivary gland carcinoma and non-advanced lateral OTSCC patients. The performed neck dissection procedure for the cN0 neck is completely different throughout the many treatment facilities, and the corresponding literature often gives, if any, only contradicting recommendations. Concerning the various forms of salivary gland carcinomas, for example, no concise guideline exists to facilitate the decision for which entities and to what extent END is necessary. The same is true of END and its indication regarding unilateral early-stage OTSCCs. Two main concurring concepts of END treatment are widely prevalent: unilateral and bilateral END. The different variations of treatment for the above-mentioned cases are, to date, non-evidence-based and are often just eminence-based decisions. The work presented in this thesis arose from just these discussed disputes concerning the correct forms of END treatment. The performed research regarding the indications of END in two different patient collectives, namely containing salivary gland carcinoma and early stage unilateral OTSCC patients, led to the publication in peer-reviewed international journals. The two articles, which are the basis of this work, will be presented in the following chapters.

2. Materials and methods

In both original research papers, a retrospective cohort study was designed and implemented. All the research was performed in accordance with the Declaration of Helsinki, and data analysis was approved by the local ethics committee of the Technical University Munich, TUM (registration numbers 2777/10 and 383/15).

2.1. Study design

2.1.1. Original research article: “Head and neck salivary gland carcinomas--elective neck dissection, yes or no?”

To address the research purpose, the study was designed as a retrospective cohort study based on histopathologic data of relevant patients. Data were obtained via the university’s interdisciplinary board for head and neck tumors. They were screened for age, gender, tumor entity, localization, grade, and TNM status [Sobin 2010].

2.1.2. Original research article: “Elective neck dissection in unilateral carcinomas of the tongue – unilateral vs. bilateral approach”

To address the raised questions concerning the benefit and optimal extent of END in patients with unilateral OTSCC, a retrospective cohort study was designed and implemented. The study was based on the histopathologic data of relevant patient cases. For the purpose of this research, the patient groups were distinguished from each other based on the treatment that they had received: the obtained data had to be acquired from two different institutions, each one performing a different therapeutic procedure. The Department of Oral and Maxillofacial Surgery of the Klinikum rechts der Isar of the Technical University Munich performed unilateral END treatment and the cooperating Department of Oral and Maxillofacial Surgery of the Ludwig-Maximilians University Munich performed a bilateral END approach. Relevant patient data were obtained via the university interdisciplinary boards for head and neck tumors and were screened retrospectively for matching criteria. Additional clinical data of indexed patients were then acquired via the university clinical file management systems in both institutes. The gathered data were screened for information concerning patient age, gender, preoperative staging results, surgical reports, histopathologic findings (e.g., TNM stage [Sobin 2010]), interdisciplinary tumor board recommendations, and postoperative treatment procedures.

2.2. Study sample

2.2.1. Original research article: “Head and neck salivary gland carcinomas--elective neck dissection, yes or no?”

The study was based on all patients presenting at the Klinikum Rechts der Isar of the Technical University Munich for treatment of salivary gland malignancies from October 2006 until October 2012. The patients presented themselves during the mentioned timeframe either to the university ENT or oral and maxillofacial surgical departments. To be included into the study population, patients had to have a malignant salivary gland carcinoma as a diagnosis. Only untreated patients were included, meaning no previous ND or radiotherapy treatment was performed. All the salivary gland malignancy cases were presented to the interdisciplinary board for head and neck tumors. Following this interdisciplinary board discussion, primary tumor surgery and subsequent ND were performed whenever possible. The ND treatment was carried out in all patients, i.e., those with clinically negative lymph nodes (cN0) and with clinically positive lymph nodes (cN+). The standard therapeutic procedure included preoperative imaging followed by surgical intervention. The surgical procedure started with the resection of the primary tumor lesion and was performed with the high respect for the guarantee of sufficient safety margins. The primary resection was followed by an ipsilateral ND from levels I to III with rapid-frozen sections being taken for direct histopathologic examination. If rapid-frozen sections of levels II and III showed signs of lymph node tumor invasion, the surgery was extended, and level V on the ipsilateral neck and levels I to III on the contralateral side of the neck were included. The contralateral ND was omitted in patient cases with positive rapid-frozen sections from primary tumors of the parotid or submandibular gland, because of the described infrequent contralateral metastasis. These specific patient cases received thorough tumor follow-up, which consisted of computed tomographic scans every 6 months during the first 2 years after diagnosis. After this two-year period, CT scans are performed once a year for another 5 years. In general, all treated patients received ND treatment; this was only omitted in patient cases with a poor overall health status (e.g., patients at a very advanced age), thus denying surgical or anesthetic interventions. ND treatment was also omitted if patients declined to give consent for therapy. The postoperative treatment process was again outlined by another presentation of the patient to the interdisciplinary head and neck tumor board with regard to the now available lymph node and primary tumor results of the final detailed histopathologic examination. Postoperative radiotherapy was performed if recommended as a postoperative treatment, but it was not used as primary treatment strategy. The described tumor surgery procedure is illustrated in Figure 1 of the corresponding original research article and in **Figure 7** of this thesis.

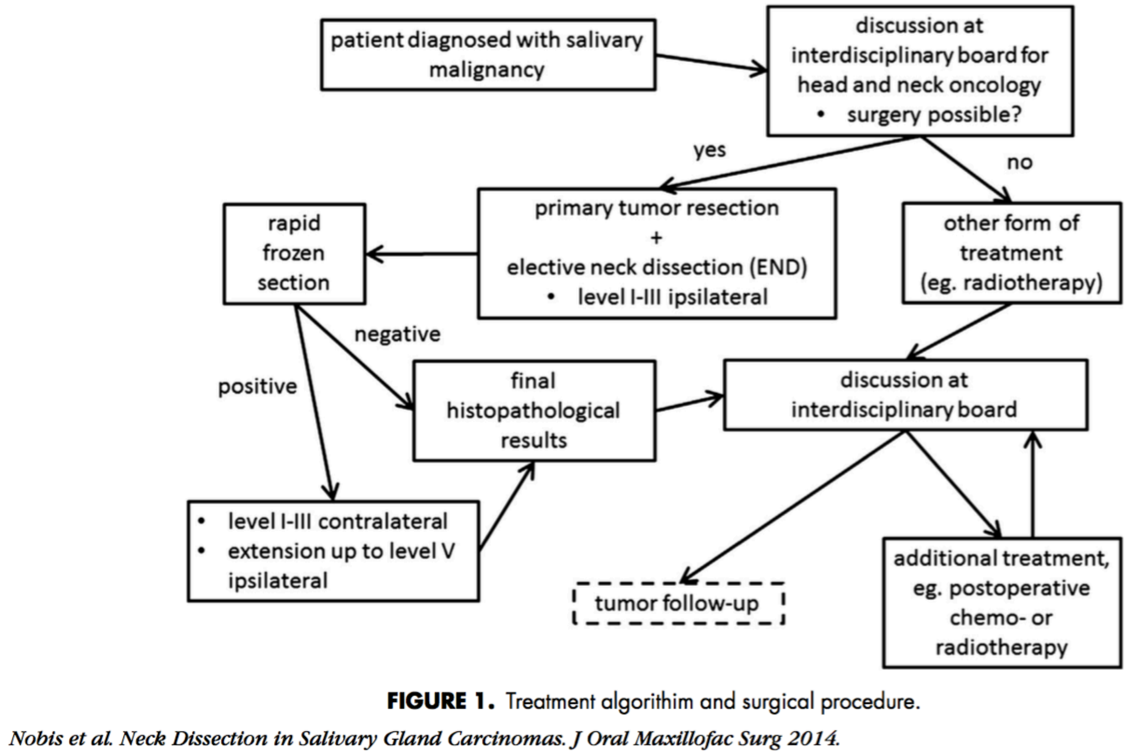

Figure 7: *Treatment algorithm and surgical procedure for the management of salivary gland carcinoma patients*

Figure is from the corresponding publication of [Nobis 2014].

2.2.2. Original research article: “Elective neck dissection in unilateral carcinomas of the tongue – unilateral vs. bilateral approach”

The study was based on two cohorts of OTSCC patients that were distinguished from each other in the form of the END treatment performed. All patients presenting to one of the two departments for treatment of T1-T2 OTSSC were included into the study. The primary tumor lesion had to be strictly unilateral, i. e., had to be limited to only one side of the tongue. Thus, the primary tumor lesion was not allowed to cross the tongue’s midline. All included patients of the first participating department (Department of Oral and Maxillofacial Surgery of the Klinikum Rechts der Isar of the Technical University Munich) presented themselves for tumor treatment between December 2006 and July 2015. In the second contributing department (Department of Oral and

Maxillofacial Surgery of the Ludwig-Maximilians University Munich), the included patients presented themselves for treatment between February 2007 and April 2015. The treatment strategy in both departments featured preoperative imaging. At the first department (TUM), the preferred strategy consisted of surgical removal of the primary tumor lesion and the following ipsilateral neck dissection of the ipsilateral lymph node levels I-III. In the second department (LMU), the preferred END treatment protocol favored the removal of lymph node levels I-III on both sides of the neck. At the department treating patients with ipsilateral END (TUM), intraoperative rapid-frozen sections were taken from all patients for direct histopathologic examination. If signs for lymph node tumor invasion were found in any of the examined lymph nodes, ND was extended. In this case, the levels IV-V of the ipsilateral neck and the levels I-III of the contralateral neck side were included in the surgery. Tumor aftercare was again outlined after a presentation to the interdisciplinary board for head and neck tumors with the now available final and detailed results of the histopathologic examination of the lymph nodes and tumors. Aftercare usually featured continuous clinical controls every 3-6 months and a CT scan each year. The described procedures and the distribution of patient cases between the two departments is further illustrated in **Figure 8** of the corresponding original research article.

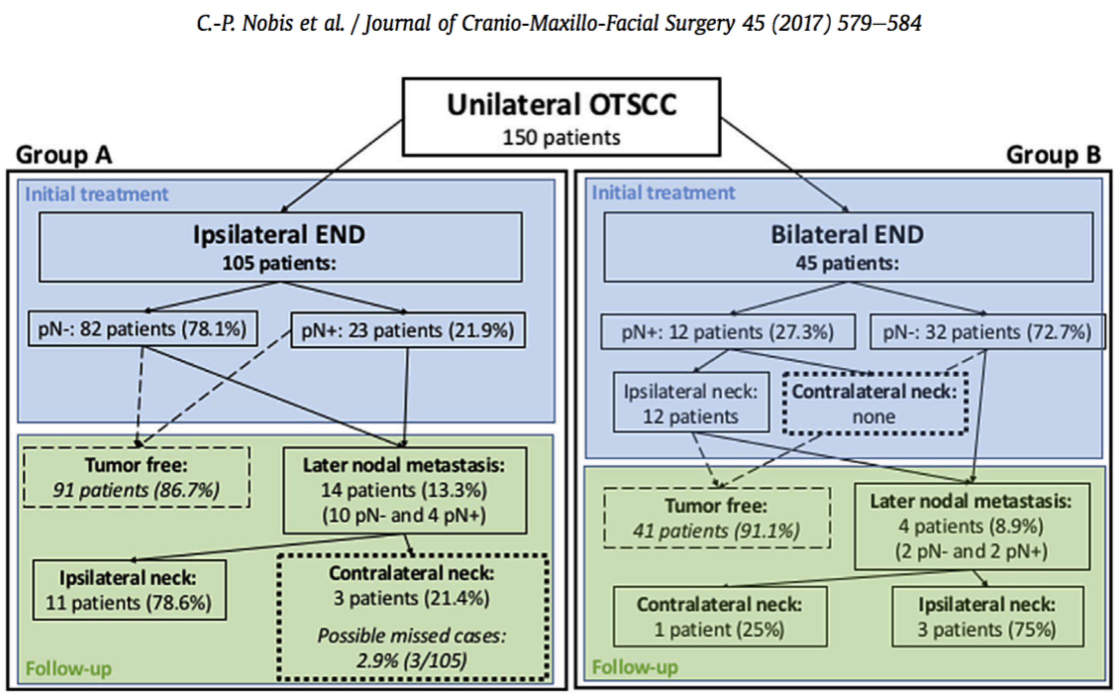

Figure 8: *The surgical procedure and distribution of patient cases.*

Figure is from the corresponding publication of [Nobis 2017].

2.3. Statistical analysis

2.3.1. Original research article: “Head and neck salivary gland carcinomas--elective neck dissection, yes or no?”

The paper’s statistical analysis was performed in order to identify possible predictors of lymph node metastasis. The two examined lymph node status groups (N+ and N0) were compared with respect to age by using the t-test for two independent samples. The statistical comparisons with respect to gender, tumor location, tumor entity, anatomic region, grade, and tumor stage were carried out by χ^2-tests with 1, 3, 4, 6, and 7 degrees of freedom, respectively. Explorative p-values were two-sided, and SPSS 19.0.0 software (IBM SPSS, Inc., Chicago, IL) was used for statistical calculations. A p-value lower than 0.05 was considered as being statistically significant. The statistical analysis was performed with the kind support of the co-author Prof. Dr. Stefan Wagenpfeil, Head of the Institute for Medical Biometry, Epidemiology and Medical Informatics, University of the Saarland, Homburg/Saar, Germany.

2.3.2. Original research article: “Elective neck dissection in unilateral carcinomas of the tongue - unilateral vs. bilateral approach”

The relevant patient data from both departments was combined, and consequent statistical analysis was performed in order to obtain information concerning the rate of positive lymph nodes in the END group and concerning later nodal metastasis during follow-up. The aim was to identify possible predictors for the rate of occult or future lymph node metastasis. SPSS 22.0.0 software (IBM SPSS, Inc., Chicago, IL) was used for statistical calculations. A p-value lower than 0.05 was considered as being statistically significant. Descriptive and inferential statistics were computed by using the two-sample t-test, the χ^2-test, or Fisher’s exact test. Recurrence free survival was assessed by using the Kaplan-Meier estimator. Differences between ipsilateral and bilateral neck dissections regarding recurrence free survival were examined by using Cox proportional hazard models. All analyses were conducted by using the survival-package in R version 3.2.4 [R-Core-Team 2015, Therneau 2015]. The statistical analysis was again performed with the kind support of co-authors Jakob Schöpe, M.Sc. and Univ.-Prof. Dr. Stefan Wagenpfeil, both from the Institute for Medical Biometry, Epidemiology and Medical Informatics, University of the Saarland, Homburg/Saar, Germany.

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3.1. Original research article: “Head and neck salivary gland carcinomas--elective neck dissection, yes or no?”

In the surgical treatment of salivary gland carcinoma patients, the consensus is that, in cases of clinically positive lymph nodes (cN+), an END should be performed. However, uncertainty remains regarding patients with clinically negative lymph nodes (cN0). Because of the uncertainties concerning the extent of lymphatic metastasis of the various salivary gland carcinoma entities, we clinically advocate a strategy of surgical resection and subsequent END for all salivary gland carcinoma patients. In order to address the remaining uncertainties and to achieve evidence-based recommendations in the future, we tried to evaluate our surgical treatment. We therefore estimated the frequency of metastatic disease and, in consequence, identified factors associated with an increased risk for metastatic disease. This retrospective cohort study was developed and implemented by using patient data obtained from the university’s interdisciplinary board for head and neck tumors. The acquired data were screened for age, gender, tumor entity, localization, grade, and TNM status. Subsequent statistical analysis was performed to identify possible predictors of lymph node metastasis. The nodal status groups (N+ and N0) were compared with respect to age by t-tests; other comparisons involved χ^2-tests. We could identify 94 patients (50% female, 50% male; mean age, 59.12 years), of whom 87 had an indication for END treatment. In the postsurgical histopathologic examination, 34 patients (39%; 17 male, 17 female) were diagnosed with positive lymph nodes (pN+). The statistical analysis for nodal status produced explorative p-values (age, $p = 0.001$; gender, $p = 0.792$; anatomic region, $p = 0.114$; tumor entity, $p = 0.854$; tumor status, $p = 0.263$; grade, $p = 0.000$). In the study, we could show that all of the studied malignancies were capable of lymph node dissemination. After thorough analysis of the acquired data, no reliable preoperative predictors for lymphatic metastasis were identifiable. Because of these difficulties in safely predicting lymphatic metastasis in combination with a high rate of pN+ results in the postoperative histopathologic examination, we strongly advise the performance of END in all patients with salivary gland carcinomas.

The design, implementation and execution of the research project was the common effort of all associated authors. As doctoral candidate, first author, and corresponding author of this research article, it was my duty to do most of the work. Initially, I was given an introduction into all the details of the necessary research topics and methods, e.g., patient indexing, clinical data acquisition, the performance of orienting statistical analysis, the preparation of a research manuscript, and the skills necessary for the submission and revision process of a peer-reviewed original research article. Most of this help was provided by co-author Dr. Dr. Nils H. Rohleder and by the head of my research group and final author Prof. Dr. Dr. Kesting. Their valuable guidance therefore enabled me to perform the indexing, acquisition, gathering, and primary analysis of all of the data by myself. The secondary in-depth statistical analysis was carried out with the kind support of Prof. Dr. Wagenpfeil. A first draft version of the article was subsequently written and prepared by myself. Further improvement of the manuscript was undertaken with the valuable advice and corrections of all the associated authors. The whole study process was supervised by Prof. Dr. Dr. Wolff as head of department. Valuable ideas and consideration from the ENT point of view were added by Priv.-Doz. Dr. Scherer of the ENT department of the Klinikum rechts der Isar, Technical University Munich. Being the corresponding author of the journal article, it was my further duty to perform the whole submission and revision process of the manuscript with the *Journal of Oral and Maxillofacial Surgery*. All participating authors were involved with final proof-reading and in providing valuable hints for improvement to the article.

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3.3. Original research article: "Elective neck dissection in unilateral carcinomas of the tongue – unilateral vs. bilateral approach"

Following the previously addressed thoughts on END treatment and its specific indications, we identified another issue with remaining uncertainties concerning the necessity of END for specific patients. Currently, a dispute remains with regard to the END extent necessary for treatment of unilateral OTSCC patients. In patients with strictly unilateral early stage OTSCC (TNM stage 1 and 2), the literature lacks specific recommendations as to whether it is sufficient just to perform unilateral END or whether a bilateral treatment would be more beneficial. A logic consequence was therefore to pick up the work previously carried out on the clarification of END indication for salivary gland patients and to conduct further investigations into unilateral OTSCC patients. To address the mentioned uncertainties, we evaluated the two discussed END variations, unilateral and bilateral, to determine the optimal extent needed for sufficient oncologic treatment. A retrospective cohort study was therefore performed on patient data from the two departments of oral and maxillofacial surgery (as above), each performing a different END extent during routine oncologic treatment. All previously untreated patients from both participating departments diagnosed with early stage (pT1-2) unilateral OTSCC were included in the study. The following variables were collected and analyzed: age, gender, END type/extent, tumor localization, later nodal metastasis, and TNM status. Statistical analyses were performed, and a p-value lower than 0.05 was considered as being statistically significant. Out of the 150 patients identified for the study, 105 received unilateral END and 45 bilateral END. The rates of postoperative positive lymph nodes were 21.9% for ipsilateral END and 26.7% for bilateral END (in the bilateral END group: all positive lymph nodes on the ipsilateral neck). 14 patients of the ipsilateral group developed nodal metastasis during tumor aftercare (11 patients on the ipsilateral and 3 patients on the contralateral neck). In the bilateral group, nodal metastasis was later observed 4 times (8.9%; 3 cases ipsilateral, 1 case contralateral neck). The subsequent statistical analysis could not detect any significant differences between the two END procedures. As both procedures lead to similar results in the prevention or omission of possible later nodal metastasis, they seem to be two alternatives of almost equal value. In conclusion, we recommend bilateral END to be performed on a routine basis in patients with unilateral early-stage OTSCC, because of advantages regarding oncologic safety and esthetic outcome. Nevertheless, the decision for END treatment should always be based on the patient's general health status, comorbidities, and individual tumor risk profile.

The design, implementation, and execution of the research project was again a common effort of all associated authors. As doctoral candidate, first author, and corresponding author of this research article, it was again my duty to carry out most of the presented work. The gained knowledge from the previous research article enabled me to start immediately with the research task. Guidance during the process of patient data acquisition was kindly given by co-author Priv.-Doz. Dr. Dr. Otto and by final author and head of my research group Prof. Dr. Dr. Kesting. The data of patients treated at the Department of Oral and Maxillofacial Surgery of the Klinikum rechts der Isar of the Technical University Munich were gathered by myself. The prepared database of the 105 unilateral END cases was extended with the 45 bilateral END cases of the Department of Oral and Maxillofacial Surgery of the Ludwig-Maximilians University Munich by Tamara Grigorieva and Mohamed Alnaqbi. The secondary in-depth statistical analysis was performed with the kind support of Jakob Schöpe and Prof. Dr. Wagenpfeil. A first draft version of the article was subsequently written and prepared by myself. Further improvement of the manuscript was undertaken with the valuable advice and correction of all the associated authors. Prof. Dr. Dr. Wolff and Prof. Dr. Dr. Ehrenfeld both supervised the study process as heads of the participating departments. Valuable ideas and considerations during the preparation of the manuscript were also given by Dr. Dr. Troeltzsch. Being the corresponding author of the journal article, it was also my duty to perform the whole submission and revision process of the manuscript with the *Journal of Cranio-Maxillofacial Surgery*. All participating authors were involved with final proof-reading and in providing valuable hints for improvements to the article.

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4. Results

4.1. Rates of lymph node metastasis for salivary gland carcinomas

The rates for lymph node metastasis were based on the data of 94 patients. Out of this reviewed study population, 47 patients were female (50%), and 47 were male (50%). The mean patient age was 59.1 years (standard deviation, 16.5 years; median, 66 years; range, 11 to 89 years). 87 patients (92.6%) received END treatment, whereas 7 patients (7.4%) did not. The postoperative histopathological examination of the removed lymph node specimen revealed 53 cases (pN0: 60.9%) with tumor-free node samples and 34 (pN+: 39.1%) with signs of lymphatic metastasis. With regard to this pN+ subgroup of 34 patients, 16 of them were male (39.6%), and 18 were female (42.9%). Out of all malignancies reviewed for the study, 41 (43.6%) arose from the parotid gland, 15 (16.0%) from the submandibular gland, and 16 (17.0%) from minor salivary glands of the palate; 22 (23.4%) carcinomas had developed in the other minor salivary glands of the oral cavity. With regard to tumor entities, 30 patients (31.9%) were diagnosed with mucoepidermoid carcinoma, which was the most frequently observed; 22 (23.4%) were adenocarcinomas, 19 (20.2%) adenoid cystic carcinomas, 7 (7.4%) acinic cell carcinomas, and 16 (17.0%) were other, less common, salivary malignancies. In view of positive nodal status and possible influencing variables, the following observations could be made: a comparison of patient gender and relating nodal status led to 17 male (50.0%) and 17 female (50.0%) pN+ patients. Comparing primary tumor location and positive lymph node status, 14 cases (41.2%) showed a parotid gland primary tumor, 7 (20.6%) a submandibular gland tumor, 2 (5.9%) a tumor of the minor salivary glands of the palate, and 11 (32.4%) a tumor of the minor glands of the remaining oral cavity. With regard to positive lymph nodes and salivary gland tumor entities, mucoepidermoid carcinoma yielded 12 cases (35.3%), adenocarcinoma 8 cases (23.5%), adenoid cystic carcinoma 7 cases (20.6%), and acinic cell carcinoma 1 case (2.9%), and 6 cases (17.6%) were other salivary gland carcinoma entities. A comparison of the pN+ patients with the remaining TNM categories led to the following results: 12 (35.3%) pN+ patients were T1, 11 (32.4%) were T2, 8 (23.5%) were T3, and 3 (8.8%) were T4. The grading of tumors was distributed in the pN+ group as follows: 3 (10.0%) were G1, 7 (23.3%) were G2, 1 (3.3%) was G2 to G3, 18 (60.0%) were G3, and 1 (3.3%) was G4. The performed statistical analysis calculated explorative p-values in relation to nodal status. These were 0.001 for age, 0.792 for gender, 0.114 for anatomic region, 0.854 for tumor entity, 0.263 for tumor status, and 0.000 for tumor grade. Moreover, in the subgroup of 11 patients diagnosed with a G1 mucoepidermoid carcinoma, none showed lymph node metastasis in the final histopathologic examination. The results are also given below in the table from the original research article, in **Figure 9**.

Table 1. PATIENT DEMOGRAPHICS

Characteristics	Total (n = 87) n	Total (n = 87) %	ND Positive (n = 34) n	ND Positive (n = 34) %	ND Negative (n = 53) n	ND Negative (n = 53) %	Explorative *P* Value
Age (yr), mean ± SD	58.43 ± 16.820		65.21 ± 14.047		54.08 ± 17.127		.001
Gender							.792
Male	45	51.7	17	50.0	28	52.8	
Female	42	48.3	17	50.0	25	47.2	
Anatomic							.114
Parotid gland	38	43.7	14	41.2	24	45.3	
Submandibular gland	14	16.1	7	20.6	7	13.2	
Minor salivary glands, palate	14	26.1	2	5.9	12	22.6	
Other minor salivary glands, cavum oris	21	24.1	11	32.4	10	18.9	
Histopathologic							.854
Mucoepidermoid carcinoma	30	34.5	12	35.3	18	34.0	
Adenocarcinoma	21	24.1	8	23.5	13	24.5	
Adenoid cystic carcinoma	16	18.4	7	20.6	9	17.0	
Acinic cell carcinoma	6	6.9	1	2.9	5	9.4	
Other carcinomas	14	16.1	6	17.6	8	15.1	
Tumor status (n)	81		34		47		.263
T1	35	43.2	12	35.3	23	48.9	
T2	25	30.9	11	32.4	14	29.8	
T3	12	14.8	8	23.5	4	8.5	
T4	9	11.1	3	8.8	6	12.8	
Grade (n)	65		30		35		.000
G1	24	36.9	3	10.0	21	60.0	
G2	15	23.1	7	23.3	8	22.9	
G2-3	1	1.5	1	3.3	0	0	
G3	24	36.9	18	60.0	6	17.1	
G4	1	1.5	1	3.3	0	0	

Abbreviations: ND, neck dissection; SD, standard deviation.

Nobis et al. Neck Dissection in Salivary Gland Carcinomas. J Oral Maxillofac Surg 2014.

Figure 9: *Characteristics of the salivary gland carcinoma patients*

Figure is from the publication of [Nobis 2014].

4.2. Rates of lymph node metastasis in unilateral early stage OTSCC

The rates of lymph node metastasis are based on the data of a study population of 150 patients who had been diagnosed with unilateral OTSCC and had not received any previous treatment. 83 patients were male (55.3%), 67 patients were female (44.7%). The mean patient age was 59.3 years (median: 60 years, SD: 14.5, range: 19-86 years). The location of the primary tumor lesion was on the left side of the tongue in 75 cases (50.7%) and on the right side of the tongue in 73 cases (49.3%). 105 patients (70%) of the study population received an ipsilateral END from levels I-III (left neck side: 57 patients, 54.3%; right neck side: 48 patients, 45.7%) and 45 patients (30%)

received a bilateral END. Later nodal metastasis was observed in 18 patients (12%), the location being, in 14 cases (9.3%), on the ipsilateral side of the neck and, in 4 cases (2.7%), on the contralateral side of the neck. The mean time until development of delayed nodal metastasis was 21.6 months (range: 4-79 months; median: 11.5 months). In the postoperative histopathologic examinations, 115 patients (76.7%) did not show any signs of lymph node infiltration (pN-), and 35 patients (23.3%) did show positive lymph nodes (pN+). An analysis of the TNM status led to the following results: 105 patients (70.5%) had a T1 tumor, and 44 patients (29.5%) had a T2 tumor. Tumor grading was distributed as follows: 29 (20.4%) patients G1, 1 (.7%) patient G1-2, 87 (61.3%) patients G2, 4 (2.8%) patients G2-3, and 21 (14.8%) patients G3. The total study population of 150 patients was divided into two study groups A and B, depending on whether END had been performed or not. The population of study group A consisted of 105 patients (70%), all of which had been treated with unilateral END of levels I-III. 63 patients (60%) of this group were male, and 42 patients (40%) were female, and their mean age was 60.9 years (median: 61 years, SD: 14.6, range: 19-86 years). The primary malignancy originated, in 58 cases (55.2%), from the left side of the tongue and, in 47 cases (44.8%), from the right side of the tongue. Out of the 105 included patients in group A, 91 patients (86.7%) stayed tumor-free until the end of the study (July 2015). A delayed cervical nodal metastasis could be observed in 14 patients (13.3%), and in 11 of them, the nodal metastasis was on the same side as the primary lesion (10.5%), whereas in 3 cases, it was on the contralateral side (2.9%). The mean time until the observation of delayed nodal metastasis (of the 14 affected patients in group A) was 18.43 months (range: 4-79 months; median: 11.5 months). With regard to adjuvant tumor therapy in group A, 77 patients (73.3%) were released into tumor follow-up and were not recommended any adjuvant therapy. 23 patients (21.9%) were advised to undergo further adjuvant radiotherapy (RTx), and 4 patients (3.8%) were advised to undergo combined radio- and chemotherapy (RCTx). Adjuvant chemotherapy (CTx) was advised in one single case (1.0%). The ipsilateral END from levels I-III was performed in all 105 patients of group A, 57 (54.3%) times on the left side of the neck and 48 times (45.7%) on the right side of the neck. The standard procedure of END therapy featured a direct histopathologic examination of the acquired rapid-frozen sections, that were taken during lymph node dissection. If the examination provided evidence for malignant lymph node infiltration, the END was extended to levels IV and V on the ipsilateral side and to levels I-III on the contralateral side. With regard to the 105 treated patients of group A, 92 (93.9%) were found to have tumor-free rapid-frozen sections, and 6 of them (6.1%) showed tumor-positive sections. All surgically acquired lymph node specimens were subjected to detailed histopathologic diagnostics. In these final examination results, 82 patients (78.1%) did not show any evidence for lymph node infiltration (pN-). In contrast, 23 patients (21.9%) did show malignant lymph node infiltration (pN+). With regard to the TNM status of group A, 75 patients (72.1%) had a tumor classified as T1 and 29 (27.9%) a tumor classified as T2. Tumor grading was distributed as follows: 22 (22.4%) were G1, 1 (1%) was G1-2, 63 (64.3%) were G2, 4 (4.1%) were G2-3, and 8 (8.2%) were G3. With regard to lymph node status in the post-operative histopathologic results and development of nodal metastasis during the disease, 4 patients with later nodal metastasis were found to be pN+ (28.6%) and 10 patients pN- (71.4%). Out of the 14 patients with the development of later nodal metastasis (13.3%), 7 patients (50%) were diagnosed with a T1 and 7 patients (50%) with a T2 primary tumor. The tumor grading in the 14 later nodal metastasis patients was distributed as follows: 2 patients (14.3%) were G1, 10 patients (71.4%) were G2, 1 patient (7.1%) was G2-3, and 1 patient (7.1%) was G3. With regard to the 23 patients (21.9%) with positive lymph node results in the postoperative histopathologic findings, 12 (52.2%) had a T1 and 11 (47.8%) a T2 primary tumor. The grading in this group was distributed as follows: 1 patient (4.3%) G1, 17 (73.9%) G2, 3 (13.0%) G2-3, and 2 (8.7%) patients G3. The study population of group B included 45 patients (30%), all of which were treated with a bilateral END of levels I-III. 20 of these patients (44.4%) were male, and 25 of them (55.6%) were female. The mean age of patients was 55.6 years (median: 55 years, SD: 13.9, range: 30-79 years). The primary tumor was located on the left side of the tongue in 17 patients (39.5%) and on the right side in 26 patients (60.5%). With regard to all included patients of group B, 41 (91.1%) remained tumor-free until the end of the study. A nodal metastasis in the further course of the disease was observed in 4 patients (8.9%); in 3 times, it was on the ipsilateral, and once, it was on the contralateral side of the neck. In 3 patients, the nodal metastasis was observed on the same side as the primary tumor lesion (6.7%), whereas in 1 case, it was observed on the contralateral side (2.2%). The mean time until the observation of later nodal metastasis (for the 4 affected patients of group B) was 30.25 months (range: 7-54 months; median: 30 months). With regard to the postoperative tumor treatment, 34 patients (75.6%) were released into tumor follow-up, and no additional treatment was recommended. 6 patients (13.3%) were advised to undergo adjuvant radiotherapy (RTx), and 5 patients (11.1%) were advised to undergo combined radio- and chemotherapy (RCTx). All of group B received a bilateral END including levels I-III. The final postoperative histopathologic examination gave the following results: 33 patients (73.3%) did not show evidence of lymph node infiltration (pN-), whereas 12 patients (26.7%) did show signs of malignant lymph node infiltration (pN+). All positive nodes observed in the affected patients were on the ipsilateral neck; none was found on the contralateral side. With regard to the TNM status, 30 patients (66.7%) had a T1 tumor and 15 (33.3%) a T2 tumor. The grading was distributed as follows: 7 (15.9%) were G1, 24 (54.5%) were G2, and 13 (29.5%) were G3. An analysis of post-operative histopathologic lymph node status and the development of nodal metastasis in the further course of the disease led to the following observations: 2 patients with later nodal metastasis were pN+ (50%), and the remaining 2 patients were pN- (50%). In this subgroup of 4 patients with later nodal metastasis (8.9%), 2 patients (50%) had a T1 tumor and 2 patients (50%) a T2 primary tumor. The tumor grading was distributed in this subgroup as follows: 2 patients (50%) were G2, and 2 patients (50%) were G3. Out of all 12 patients (27.3%) with positive lymph node results, 4 (33.3%) had a T1 and 8 (66.7%) a T2 primary tumor. The grading in this group was: 1 patient (8.3%) G1, 4 patients (33.3%) G2, and 7 (58.3%) patients G3. The data and results are further shown in **Figure 10**.

Patient characteristics.

	Overall (N = 150)	Ipsilateral END (n = 105)	Bilateral END (n = 45)	p-Value
Age [mean ± SD]	59.3 ± 14.5	60.9 ± 14.6	55.6 ± 13.9	0.044
Sex [n (%)]				
Male	83 (55.3%)	63 (60.0%)	20 (44.4%)	0.115
Female	67 (44.7%)	42 (40.0%)	25 (55.6%)	
Later nodal metastasis [n (%)]				
None	132 (88.0%)	91 (86.7%)	41 (91.1%)	0.814
Ipsilateral	14 (9.3%)	11 (10.5%)	3 (6.7%)	
Contralateral	4 (2.7%)	3 (2.8%)	1 (2.2%)	
Adjuvant therapy [n (%)]				
None	111 (74.0%)	77 (73.3%)	34 (75.6%)	0.200
RTx	29 (19.3%)	23 (21.9%)	6 (13.3%)	
RCTx	9 (6.0%)	4 (3.8%)	5 (11.1%)	
CTx	1 (0.7%)	1 (1.0%)	0 (0.0%)	
Nodal status [n (%)]				
pN+	35 (23.3%)	23 (21.9%)	12 (26.7%)	0.674
pN−	115 (76.7%)	82 (78.1%)	33 (73.3%)	
Tumor status[a] [n (%)]				
T1	105 (70.5%)	75 (72.1%)	30 (66.7%)	0.636
T2	44 (29.5%)	29 (27.9)	15 (33.3%)	
Grading[a] [n (%)]				
G1	29 (20.4%)	22 (22.4%)	7 (15.95)	0.012
G1−2	1 (0.7%)	1 (1.0%)	0 (0.0%)	
G2	87 (61.3%)	63 (64.3%)	24 (54.5%)	
G2−3	4 (2.8%)	4 (4.1%)	0 (0.0%)	
G3	21 (14.8%)	8 (8.2%)	13 (29.9%)	
Recurrence-free survival[a] [mean (95%CI) in months]	76.1 (70.7−81.6)	75.9 (69.7−82.2)	72.3 (62.7−81.8)	

[a] Based on available cases.

Figure 10: *Characteristics of the OTSCC patients*

Figure is from the publication of [Nobis 2017].

5. Discussion

Neck dissection treatment is indisputably one of the main pillars of head and neck oncologic surgery [Ferlito 2006a, Ferlito 2006b, Robbins 2013]. Following primary tumor resection, neck dissection treatment is a means of surgical therapy in almost every form of head and neck carcinoma, depending on the entity and clinical advancement of the tumor. ND treatment is generally undisputed in patients with positive lymph nodes in preoperative staging, although determination of the suitable extent of ND is still crucial. In cases with clinically negative necks (cN0 patients) and for some malignancies of the salivary glands, ND therapy is still disputed. The high reported rates of 20-40% for occult metastasis of OSCC to the neck, as reported in the literature [Clark 2006, Fasunla 2011, Wolff 2012a, Wolff 2012b], highlight the importance of the ND treatment decision. The right balance must be achieved between oncologic safety in the light of high occult metastasis risk and the sparing of increased surgical morbidity attributable to possible overtreatment. The work in this thesis has therefore been focused on the facilitation of the process of finding these correct indications and extensions of END treatment in still disputed cases. Clarification of the indications of END treatment for the various entities of salivary gland carcinomas has been attempted [Nobis 2014], as has the elucidation of the question of the optimal extent necessary for unilateral OTSCC [Nobis 2017].

The research performed in both the above-described studies is consistent with the high rates of occult metastasis for HNSCC; in the salivary gland tumor collective, a rate of 39.5% could be observed, and in the OTSCC patient collective, a rate of 23.3% was recorded. These data thus stress the overall importance of ND treatment for head and neck tumors.

Nevertheless, a general recommendation concerning ND treatment for head and neck tumors is difficult, as this anatomic region is the possible origin of a large variety of entirely different malignancies (e.g., see **Figure 1**). Each of the groups must therefore individually be the focus of attention. In general, ND treatment is considered as an effective method for the treatment of the lymphatic spread of malignant disease. Its impact on patient survival is vital, as the regional lymphatic involvement highly decreases the viability of the patient [Hamoir 2014, Woolgar 2013].

There is not only a lack of consensus concerning the indication of ND treatment, but also with respect to its specific extent, especially when it comes to subgroup treatment. As in case of OTSCC patients, a more extensive surgical approach is usually advocated if the malignancy has begun to cross the tongue's midline. However, for early-stage tumors, this issue is controversial, with many authors advocating either uni- or bilateral approaches [Koo 2006, Lim 2007, Lim 2006]. The relevant literature is however largely in agreement; because of the mentioned high rates of occult metastasis for OSCC, most authors do at least recommend an ipsilateral END for all cN0 patients, as an increase in patient survival rates has been recorded in several studies [Franceschi 1993, Haddadin 1999, Tankere 2000].

To solve the problem of the correct ND indication, much effort has been extended into finding possible predictors of lymphatic spread. In OSCC patients, *Clark et al.* have stressed tumor thickness as being the most important predictor of occult nodal metastases and agree with the current procedure of END (levels I-III) being carried out in the majority of patients [Clark 2006]. The value of countering metastatic disease is further underlined by the presence of nodal metastasis being found to be by far the most important prognostic variable that significantly diminishes regional control and patient survival. *Sparano et al.* have identified advanced tumor thickness, perineural invasion, infiltrating-type invasion front, poor tumor differentiation, and the T2 stage as markers for an increased probability of occult neck disease [Sparano 2004]. Similar observations have been made by *Byers et al.*, who have suggested depth of muscle invasion, double DNA aneuploidy, and histologic tumor differentiation as possible markers [Byers 1998]. The present study data on OTSCC are consistent with the current literature on markers for increased risk of lymph node metastasis. Age ($p = 0.044$) and tumor grade ($p = 0.012$) have been shown above as possible predictors for occult disease. The study performed on a salivary gland tumor patient collective has also shown tumor grade ($p = 0.000$) and advanced age ($p = 0.001$) to be related to an elevated metastasis risk. However, these 2 factors have not proven to be sufficient to serve as safe predictors in the preoperative setting when the indication in favor or against END is made. In particular, with regard to the many diverse entities of salivary gland carcinomas, the finding of a safe and reliable predictor of lymph node metastasis is almost impossible. The marker would have to be entity-specific, but even the diagnosis of the exact entity is often unsafe in preoperative diagnostics. A high risk for patients would always remain, and a curative treatment approach could be threatened by possible lymph node metastasis, if ND is omitted because of errors in preoperative diagnostics.

Another possible way to address the discussed issues of ND indication and extension would be an approach based on an examination of sentinel lymph nodes. The need and extent of ND treatment could be verified preoperatively through a sentinel lymph node biopsy (SLNB). This method could allow the performance of a more individual staging in each affected patient and might therefore lead to a more custom-tailored recommendation regarding further surgical interventions. It could provide the patient with just the exact individual surgical intervention necessary and spare exaggerated surgical morbidity. The usage of sentinel lymph nodes as a basis of a decision for whether a full lymph node dissection is necessary has proven to be a feasible solution in other medical fields, such as in breast cancer treatment [D'Angelo-Donovan 2012]. This success has led to many attempts to transfer this concept into the field of oral and maxillofacial surgery. Studies have suggested that SLNB is useful for the management of cN0 patients, especially as an optimization of the preoperative staging procedure [Ross 2004]. An advantage of SLNB is that both neck sides can be staged [Pezier 2012]. Another of the main reasons in favor of this method is the observed better quality of life and the reduction in postsurgical complications [Murer 2011, Schiefke 2009]. The drawbacks of this low-morbidity approach are the higher false-negative rates and the lower sensitivity in comparison with classic END. In summary, sentinel lymph node mapping has shown some efficacy for carcinomas of the oral cavity, but it is associated with remaining technical difficulties (e. g., the identification of multiple sentinel nodes, shine-through interferences) [Robbins 2013], making it a treatment option that should be evaluated and improved further. After a reduction of its disadvantages, it surely could develop into a valuable staging option in the future.

Another approach for solving the issues of the correct END indication might lie in the efforts undertaken to predict future metastasis risk by molecular characterization. For example, *Rickman et al.* [Rickman 2008] have tried to predict the future metastasis of HNSCC based on transcriptome and genome analysis by microarrays. Their study showed that the most significantly altered transcripts between metastasis and non-metastasis groups were significantly associated to metastasis-related functions, e. g., adhesion, mobility, and cell survival. Several genomic modifications could be detected that were significantly associated with metastatic spread (e.g., gains at 4q11–22, Xq12–28 and losses at 11q14–24, 17q11). In the current clinical setting, methods such as these are still in development and under further examination but could advance into helpful diagnostic tools in the future.

The presented study on salivary gland carcinoma patients had the advantage of featuring a relatively large number of patients treated in a realistic standard clinical setting. Unfortunately, the examined number of patients did not prove to be sufficient to limit the population to a single regional or histologic group. Therefore, no recommendations on the handling of specific salivary gland carcinoma subgroups can be given, and uncertainties remain, as no reliable predictors have been established. This leaves opportunities for future research with larger patient groups, and hopefully recommendations for subtype handling can be provided in the future with the help of the contributions made here. The study of OTSCC patients has shown that both END procedures, namely uni- and bilateral, are of a similar efficiency in addressing lymph node metastasis. This is also the main drawback of the present research, as no significant differences could be detected, and thus, the decision could not be narrowed down to a more favorable surgical approach. The key question of whether the observed slight differences between the two procedures would justify a distinct recommendation concerning all OTSCC patients remains difficult to answer. A further evaluation with larger study populations will certainly be helpful and might, with contribution of the presented work, lead to concise guidelines in the future.

As outlined above, many uncertainties remain regarding the extent and indications of ND in head and neck malignancies. The studies presented in this thesis had the aim of providing recommendations for ND treatment in specific head and neck tumor subgroups. These will be discussed further in the following paragraphs.

5.1. Recommendations concerning END treatment

5.1.1. Salivary gland carcinomas

The presented research focusing on the optimal END treatment for salivary gland carcinomas has led to the conclusion that neck dissection in combination with primary tumor surgery is a sensible and powerful tool in countering this malignant disease and in preventing already existing or future lymphatic dissemination. The large variety of the many different malignant entities, which all showed the capability of developing lymphatic metastasis in the presented research work, stress the importance of END treatment. As a conclusion from the patient data, we advocate the strategy of surgical resection and END for all cases of salivary gland carcinoma. This means that the END procedure is not only performed in patients with clinically positive lymph nodes (cN+), but also in clinically negative patients (cN0). The aim of this treatment regime is to address the uncertainty in the extent and presumably high risk of occult lymph node metastasis. In our study data, 39.5% of the patients had positive lymph node results, and in addition, no group could be identified in which this surgical method was expendable. Importantly, occult metastasis occurred in even low-grade and small tumors (e.g., more than 30% of patients with positive lymph nodes had a grading of G2 or lower). The probability of occult or future lymph node metastasis is therefore difficult to estimate. Unfortunately, no reliable predictor for preoperative risk estimation could be identified. Although grading ($p = 0.000$) and advanced age ($p = 0.001$) could be related to an elevated risk, these variables are not sufficient to serve as reliable predictors in preoperative staging. Within clinical routine, information on tumor grading is usually only available together with the final postoperative histopathological tumor results, and patient age alone is a variable too weak for a sensible decision to be made. Furthermore, there is not only uncertainty in the diagnosis of the primary entity, but also in the estimation of the preoperative clinical lymph node status. In conclusion, salivary malignancies make up a heterogeneous and largely diverse entity of malignant tumors. The therapy of this disease remains challenging, not only because of its relative rareness in the routine clinical setting, but also because of the lack of specific treatment guidelines and reported patient data of larger study populations. The continued gathering and analysis of further relevant tumor data are therefore vital, and future findings have to be compared. This may lead to the achievement of evidence-based recommendations for the treatment of salivary malignancies and ultimately even to concise guidelines for the therapy of the various individual subtypes. The above research work has shown, in agreement with the current literature, the overall high rates of occult lymph node metastasis and the lack of reliability in predicting lymphatic dissemination spread, making END a highly favorable tool of treatment. The widely-practiced strategy of direct surgical resection of the primary tumor lesion in combination with END only adds slightly to patient morbidity. The research stresses the importance of this method for all patients with salivary gland malignancies, and its omission can be deduced to lead to a possible highly-increased risk of lymph node metastasis. The failure at an early stage to counter already present and possible future lymph node metastasis might have a huge impact on the further prognosis of the patient and ultimately on patient survival.

5.1.2. Early stage unilateral OTSCC

High rates of 20-40% for occult metastasis are not only observed in salivary gland carcinomas, but also for OSCC patients in general. The current treatment guidelines therefore recommend the performance of an ipsilateral END in patients, rather than just careful clinical observation. This method is widely accepted for OSCCs in general, but as with the different forms of salivary gland carcinomas, uncertainties remain regarding carcinomas of the tongue. The more advanced malignancies, i.e., those that have already started to cross the tongue’s midline, are commonly addressed by a more severe surgical intervention, e.g., bilateral END. This strategy may be advocated in extended forms of OTSCC as a standard elective procedure, but for less advanced cases, much doubt and debate remain. One aim of the presented research was therefore to help facilitate decisions regarding the optimal necessary extent of END in early stage unilateral OTSCCs, e.g., as to whether unilateral or bilateral END is the more sensible treatment method in early stage (T1/T2) unilateral OTSCC. The gathering and analysis of relevant patient data should ultimately contribute to the future goal of developing evidence-based treatment guidelines for this specific subgroup. To achieve this goal, we reviewed the retrospective study data from two individual departments for oral and maxillofacial surgery, each one advocating a different END approach.

In general, positive lymph nodes were found in 35 patients (23.3%) from 150 participants in both study groups. 18 patients (12%) developed lymph node metastasis during the further course of their disease. 14 of these patients (13.3%) were in the solely ipsilateral END treatment group and 4 patients (8.9%) in the treatment group with bilateral END. With regard to the unilateral END group, 11 patients (78.6%) had a later nodal metastasis on the ipsilateral side, whereas in 3 cases (21.4%), it occurred on the contralateral side. These specific patients might therefore have benefitted from a more extensive END (e.g., 2.9%; 3/105 patients). In the bilateral END group, positive lymph nodes were found in 12 patients (26.7%,), all of which were found on the ipsilateral side of the neck. No lymphatic dissemination could be observed on the contralateral side. These would probably be patients showing a possible benefit from the bilateral END approach. Taking a closer look at the 4 patients (8.9%) with later nodal metastasis from the bilateral END group, 3 had their metastasis on the ipsilateral neck (75%) and 1 on the contralateral neck (25%). Both END methods were observed to achieve similar results in all evaluated parameters and variables. In addition, no statistical differences could be detected, especially concerning metastasis-free survival. Even with the help of the presented patient data, a clear answer to the question as to which form of END is more sensible in early stage OTSCC therefore remains challenging, and further extended research regarding this this topic would clearly be helpful. However, as a conclusion from our research, we can in general recommend a bilateral END for strictly unilateral OTSCC. As with the salivary gland carcinomas, we could observe a high value for occult metastasis of 23.3%. Preoperatively, they showed only slight clinical tumor progression, and thus, a directly more extensive treatment approach may be justified. The data clearly establish that a malignant spread to the contralateral lymph nodes is possible even at early stages. A patient, being in good general health and most likely not at high risk of predictable sequelae from the extended surgical treatment might therefore benefit from a direct bilateral END approach. As the observed differences between unilateral and bilateral END are only minor, the omission of the additional neck side in medically constrained patients would in consequence have little harmful impact. In standard patients, however, the additional possible oncologic benefit might nevertheless justify the decision to undertake a bilateral procedure, even if the evidence for it only has minor strength.

6. Conclusions

The main goal of the presented original research articles on which this thesis is based was to help clarifying the indication and necessary extent of ND treatment for specific head and neck carcinoma subgroups. ND in general is viewed as an effective tool for targeting the high risk of occult lymph node metastasis in head and neck tumors and improves patient survival. Nevertheless, when the various patient subgroups are considered, much controversy is still present throughout the literature. Even today, many surgical ND treatment approaches are not yet evidence-based but are often just eminence-based with regard to the experience of the relevant department. In order to help to establish concise recommendations for ND treatment, this work focused on two HNSCC subgroups: salivary gland malignancies and unilateral early-stage OTSCC. In cases of the salivary gland malignancies, the aim was to find out which of the various entities need an END approach and which do not. The presented study showed that all the examined malignancies were capable of lymph node dissemination, and our thorough analysis revealed that the detection of reliable preoperative predictors for lymphatic metastasis was not possible. This finding, in combination with the current difficulties in safely predicting lymphatic metastasis and the overall high rates of lymph node metastasis, suggests that END can be advised as a primary treatment for all patients with salivary gland carcinomas, no matter what the specific tumor entity is. The study on unilateral non-advanced OTSCC demonstrated that both ND treatment procedures were of similar capability in preventing later nodal metastasis. The two methods were both established as being valuable alternatives, with only slight differences. In conclusion and with recognition of these differences, bilateral END can be recommended as a standard ND procedure, because of its advantages with regards to oncologic safety and esthetic outcome. Nevertheless, the decision for the exact END treatment has always to be made in patient-specific manner, i.e., in accordance with the general health status, comorbidities, and individual tumor risk profile of the patient. The two studies presented in this thesis had the goal of facilitating the decisions for ND treatment of head and neck carcinoma patients and might add to the availiable data concerning two clinically relevant subgroups. The decision regarding the extent of END for OTSCC and the necessity of END for salivary gland malignancies can therefore be made in future with the knowledge gained from more evidence-based background research.

References

Andry, G., Hamoir, M., Locati, L.D., Licitra, L., Langendijk, J.A. Management of salivary gland tumors. Expert review of anticancer therapy 12 (2012) 1161-1168

Bagan, J.V., Scully, C. Recent advances in Oral Oncology 2007: epidemiology, aetiopathogenesis, diagnosis and prognostication. Oral Oncol 44 (2008) 103-108

Balaram, P., Sridhar, H., Rajkumar, T., Vaccarella, S., Herrero, R., Nandakumar, A., Ravichandran, K., Ramdas, K., Sankaranarayanan, R., Gajalakshmi, V., Munoz, N., Franceschi, S. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer 98 (2002) 440-445

Barnes, E.L., Eveson, J.W., Reichart, P., Sidransky, D. (eds) "World Health Organization classification of tumours: pathology & genetics. Head and neck tumours“, 3rd Edition, IARCPress, Lyon, 2005

Bell, R.B., Dierks, E.J., Homer, L., Potter, B.E. Management and outcome of patients with malignant salivary gland tumors. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 63 (2005) 917-928

Bjorndal, K., Krogdahl, A., Therkildsen, M.H., Overgaard, J., Johansen, J., Kristensen, C.A., Homoe, P., Sorensen, C.H., Andersen, E., Bundgaard, T., Primdahl, H., Lambertsen, K., Andersen, L.J., Godballe, C. Salivary gland carcinoma in Denmark 1990-2005: a national study of incidence, site and histology. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 47 (2011) 677-682

Bjorndal, K., Krogdahl, A., Therkildsen, M.H., Overgaard, J., Johansen, J., Kristensen, C.A., Homoe, P., Sorensen, C.H., Andersen, E., Bundgaard, T., Primdahl, H., Lambertsen, K., Andersen, L.J., Godballe, C. Salivary gland carcinoma in Denmark 1990-2005: outcome and prognostic factors. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 48 (2012) 179-185

Bocca, E., Pignataro, O. A conservation technique in radical neck dissection. The Annals of otology, rhinology, and laryngology 76 (1967) 975-987

Brierley, J.D., Gospodarowicz, M.K., Wittekind, C. (eds) "TNM Classification of Malignant Tumours“, 8th Edition, Wiley-Blackwell, Oxford, UK, 2016

Butlin, H.T. Diseases of the tongue. Cassel, London (1885)

Byers, R.M. Modified neck dissection. A study of 967 cases from 1970 to 1980. American journal of surgery 150 (1985) 414-421

Byers, R.M., El-Naggar, A.K., Lee, Y.Y., Rao, B., Fornage, B., Terry, N.H., Sample, D., Hankins, P., Smith, T.L., Wolf, P.J. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? Head Neck 20 (1998) 138-144

Clark, J.R., Naranjo, N., Franklin, J.H., de Almeida, J., Gullane, P.J. Established prognostic variables in N0 oral carcinoma. Otolaryngol Head Neck Surg 135 (2006) 748-753

Conway, D.I., Petticrew, M., Marlborough, H., Berthiller, J., Hashibe, M., Macpherson, L.M. Socioeconomic inequalities and oral cancer risk: a systematic review and meta-analysis of case-control studies. Int J Cancer 122 (2008) 2811-2819

D'Angelo-Donovan, D.D., Dickson-Witmer, D., Petrelli, N.J. Sentinel lymph node biopsy in breast cancer: a history and current clinical recommendations. Surg Oncol 21 (2012) 196-200

Dias, F.L., A. Lima, R.A., Cernea, C.R. Management of Tumors of the Submandibular and Sublingual Glands. (2007) In: "Salivary Gland Disorders", Myers EN, Ferris RL (eds), Springer-Verlag Berlin, Heidelberg, 2007, pp 339-376

Fasunla, A.J., Greene, B.H., Timmesfeld, N., Wiegand, S., Werner, J.A., Sesterhenn, A.M. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol 47 (2011) 320-324

Fein, D.A., Mendenhall, W.M., Parsons, J.T., McCarty, P.J., Stringer, S.P., Million, R.R., Cassisi, N.J. Carcinoma of the oral tongue: a comparison of results and complications of treatment with radiotherapy and/or surgery. Head Neck 16 (1994) 358-365

Ferlito, A., Rinaldo, A., Robbins, K.T., Silver, C.E. Neck dissection: past, present and future? The Journal of laryngology and otology 120 (2006a) 87-92

Ferlito, A., Rinaldo, A., Silver, C.E., Shah, J.P., Suarez, C., Medina, J.E., Kowalski, L.P., Johnson, J.T., Strome, M., Rodrigo, J.P., Werner, J.A., Takes, R.P., Towpik, E., Robbins, K.T., Leemans, C.R., Herranz, J., Gavilan, J., Shaha, A.R., Wei, W.I. Neck dissection: then and now. Auris, nasus, larynx 33 (2006b) 365-374

Franceschi, D., Gupta, R., Spiro, R.H., Shah, J.P. Improved survival in the treatment of squamous carcinoma of the oral tongue. American journal of surgery 166 (1993) 360-365

Gale, N., Cardesa, A., Zidar, N. TNM Grading. (2006a) In: "Pathology of the Head and Neck", Cardesa A, Slootweg PJ (eds), 1st Edition, Springer-Verlag Berlin, Heidelberg, 2006a, p 220

Gale, N., Zidar, N. Benign and Potentially Malignant Lesions of the Squamous Epithelium and Squamous Cell Carcinoma. (2006b) In: "Pathology Of The Head And Neck", Cardesa A, Slootweg PJ (eds), 1st Edition, Springer-Verlag Berlin, Heidelberg, 2006b, pp 1-29

Glenny, A.M., Furness, S., Worthington, H.V., Conway, D.I., Oliver, R., Clarkson, J.E., Macluskey, M., Pavitt, S., Chan, K.K., Brocklehurst, P. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane Database Syst Rev (2010) CD006387

Haddadin, K.J., Soutar, D.S., Oliver, R.J., Webster, M.H., Robertson, A.G., MacDonald, D.G. Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 21 (1999) 517-525

Hamoir, M., Schmitz, S., Gregoire, V. The role of neck dissection in squamous cell carcinoma of the head and neck. Curr Treat Options Oncol 15 (2014) 611-624

Jawdynski, F. Przypadek raka pierwotnego szyi. t.z. raka skrzelowego Volkmann'a. Wycidcie nowotworu wraz z rezekcyja tdtnicy szyjowej wspólnej i ryiy szyjowej wewndtrznej. Wyzdrowienie. Gaz Lek 8 (1888) 530-537, 554–560, 582–587

Kari, S., Alho, O.P., Jokinen, K., Hyrynkangas, K., Laara, E. Carcinoma of the oral tongue in northern Finland: trends in overall incidence and patient and tumour characteristics. J Oral Pathol Med 26 (1997) 480-483

Kesting, M.R. "Oral Cancer Surgery: A Visual Guide“, 1st Edition, Thieme Verlag, Stuttgart, 2015

Koo, B.S., Lim, Y.C., Lee, J.S., Choi, E.C. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head Neck 28 (2006) 896-901

Lim, Y.C., Choi, E.C. Unilateral, clinically T2N0, squamous cell carcinoma of the tongue: surgical outcome analysis. Int J Oral Maxillofac Surg 36 (2007) 610-614

Lim, Y.C., Lee, J.S., Koo, B.S., Kim, S.H., Kim, Y.H., Choi, E.C. Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. Laryngoscope 116 (2006) 461-465

Loree, T.R., Strong, E.W. Significance of positive margins in oral cavity squamous carcinoma. American journal of surgery 160 (1990) 410-414

Malata, C.M., Camilleri, I.G., McLean, N.R., Piggot, T.A., Kelly, C.G., Chippindale, A.J., Soames, J.V. Malignant tumours of the parotid gland: a 12-year review. British journal of plastic surgery 50 (1997) 600-608

Mardini, S., Wei, F.C., Salgado, C.J., Chen, H.C. Reconstruction of the reconstructive ladder. Plastic and reconstructive surgery 115 (2005) 2174

Marron, M., Boffetta, P., Zhang, Z.F., Zaridze, D., Wunsch-Filho, V., Winn, D.M., Wei, Q., Talamini, R., Szeszenia-Dabrowska, N., Sturgis, E.M., Smith, E., Schwartz, S.M., Rudnai, P., Purdue, M.P., Olshan, A.F., Eluf-Neto, J., Muscat, J., Morgenstern, H., Menezes, A., McClean, M., Matos, E., Mates, I.N., Lissowska, J., Levi, F., Lazarus, P., La Vecchia, C., Koifman, S., Kelsey, K., Herrero, R., Hayes, R.B., Franceschi, S., Fernandez, L., Fabianova, E., Daudt, A.W., Dal Maso, L., Curado, M.P., Cadoni, G., Chen, C., Castellsague, X., Boccia, S., Benhamou, S., Ferro, G., Berthiller, J., Brennan, P., Moller, H., Hashibe, M.

Cessation of alcohol drinking, tobacco smoking and the reversal of head and neck cancer risk. Int J Epidemiol 39 (2010) 182-196

Marur, S., D'Souza, G., Westra, W.H., Forastiere, A.A. HPV-associated head and neck cancer: a virus-related cancer epidemic. The lancet oncology 11 (2010) 781-789

McMahon, J., O'Brien, C.J., Pathak, I., Hamill, R., McNeil, E., Hammersley, N., Gardiner, S., Junor, E. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg 41 (2003) 224-231

Moore, S.R., Johnson, N.W., Pierce, A.M., Wilson, D.F. The epidemiology of tongue cancer: a review of global incidence. Oral diseases 6 (2000) 75-84

Muir, C., Weiland, L. Upper aerodigestive tract cancers. Cancer 75 (1995) 147-153

Murer, K., Huber, G.F., Haile, S.R., Stoeckli, S.J. Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. Head Neck 33 (2011) 1260-1264

Murthy, V., Agarwal, J.P., Laskar, S.G., Gupta, T., Budrukkar, A., Pai, P., Chaturvedi, P., Chaukar, D., D'Cruz, A. Analysis of prognostic factors in 1180 patients with oral cavity primary cancer treated with definitive or adjuvant radiotherapy. Journal of cancer research and therapeutics 6 (2010) 282-289

National Cancer Institute (2013) Head and Neck Cancers - Fact Sheet (http://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet) Access Date: 29.07.2016

Nobis, C.P., Otto, S., Grigorieva, T., Alnaqbi, M., Troeltzsch, M., Schope, J., Wagenpfeil, S., Ehrenfeld, M., Wolff, K.D., Kesting, M.R. Elective neck dissection in unilateral carcinomas of the tongue: Unilateral versus bilateral approach. J Craniomaxillofac Surg 45 (2017) 579-584

Nobis, C.P., Rohleder, N.H., Wolff, K.D., Wagenpfeil, S., Scherer, E.Q., Kesting, M.R. Head and neck salivary gland carcinomas--elective neck dissection, yes or no? Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 72 (2014) 205-210

Olmi, P., Cellai, E., Chiavacci, A., Scolaro, T., Torricella, A., Fallai, C. Oral cavity cancer: 234 patients treated with radiotherapy alone with curative intent. Rays 13 (1988) 107-115

Pezier, T., Nixon, I.J., Gurney, B., Schilling, C., Hussain, K., Lyons, A.J., Oakley, R., Simo, R., Jeannon, J.P., McGurk, M. Sentinel lymph node biopsy for T1/T2 oral cavity squamous cell carcinoma--a prospective case series. Ann Surg Oncol 19 (2012) 3528-3533

Prince, S., Bailey, B.M. Squamous carcinoma of the tongue: review. Br J Oral Maxillofac Surg 37 (1999) 164-174

R-Core-Team (2015) R: A language and environment for statistical computing (http://www.r-project.org/) Access Date: 17.03.2017

Ramirez-Amador, V., Esquivel-Pedraza, L., Ochoa-Carrillo, F.J., Cuapio-Ortiz, A., Frias-Mendivil, M., Meneses-Garcia, A., Sanchez-Mejorada, G. Cancer of the mobile tongue in Mexico. A retrospective study of 170 patients. European journal of cancer. Part B, Oral oncology 31B (1995) 37-40

Rickman, D.S., Millon, R., De Reynies, A., Thomas, E., Wasylyk, C., Muller, D., Abecassis, J., Wasylyk, B. Prediction of future metastasis and molecular characterization of head and neck squamous-cell carcinoma based on transcriptome and genome analysis by microarrays. Oncogene 27 (2008) 6607-6622

Riedel, F., Hormann, K. [Plastic surgery of skin defects in the face. Principles and perspectives]. HNO 53 (2005) 1020-1036

Rinaldo, A., Ferlito, A., Silver, C.E. Early history of neck dissection. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 265 (2008) 1535-1538

Robbins, K.T., Clayman, G., Levine, P.A., Medina, J., Sessions, R., Shaha, A., Som, P., Wolf, G.T. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Archives of otolaryngology--head & neck surgery 128 (2002) 751-758

Robbins, K.T., Ferlito, A., Shah, J.P., Hamoir, M., Takes, R.P., Strojan, P., Khafif, A., Silver, C.E., Rinaldo, A., Medina, J.E. The evolving role of selective neck dissection for head and neck squamous cell carcinoma. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 270 (2013) 1195-1202

Robbins, K.T., Medina, J.E., Wolfe, G.T., Levine, P.A., Sessions, R.B., Pruet, C.W. Standardizing neck dissection terminology. Official report of the Academy's Committee for Head and Neck Surgery and Oncology. Archives of otolaryngology--head & neck surgery 117 (1991) 601-605

Robert Koch Institut (2015) Krebs in Deutschland 2011/2012. Mundhöhle und Rachen, vol 10 Berlin, pp 26-29

Rosenquist, K. Risk factors in oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Swed Dent J Suppl (2005a) 1-66

Rosenquist, K., Wennerberg, J., Schildt, E.B., Bladstrom, A., Goran Hansson, B., Andersson, G. Oral status, oral infections and some lifestyle factors as risk factors for oral and oropharyngeal squamous cell carcinoma. A population-based case-control study in southern Sweden. Acta oto-laryngologica 125 (2005b) 1327-1336

Ross, G.L., Soutar, D.S., MacDonald, D.G., Shoaib, T., Camilleri, I.G., Robertson, A.G. Improved staging of cervical metastases in clinically node-negative patients with head and neck squamous cell carcinoma. Ann Surg Oncol 11 (2004) 213-218

Schiefke, F., Akdemir, M., Weber, A., Akdemir, D., Singer, S., Frerich, B. Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck 31 (2009) 503-512

Scully, C. Oral cancer aetiopathogenesis; past, present and future aspects. Medicina oral, patologia oral y cirugia bucal 16 (2011) e306-311

Silver, C.E., Rinaldo, A., Ferlito, A. Crile's neck dissection. Laryngoscope 117 (2007) 1974-1977

Sobin, L., Gospodarowicz, M., Wittekind, C. (eds) "TNM-Classification of Malignant Tumors“, 7th Edition, International Union Against Cancer (UICC), New York, Brisbane, Toronto, 2010

Sparano, A., Weinstein, G., Chalian, A., Yodul, M., Weber, R. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 131 (2004) 472-476

Spiro, R.H., Huvos, A.G., Berk, R., Strong, E.W. Mucoepidermoid carcinoma of salivary gland origin. A clinicopathologic study of 367 cases. American journal of surgery 136 (1978) 461-468

Squier, C.A., Cox, P., Hall, B.K. Enhanced penetration of nitrosonornicotine across oral mucosa in the presence of ethanol. J Oral Pathol 15 (1986) 276-279

Suarez, O.N. Le probleme chirurgical du cancer du larynx. Ann Otolaryngol 79 (1962) 22-34

Talamini, R., Bosetti, C., La Vecchia, C., Dal Maso, L., Levi, F., Bidoli, E., Negri, E., Pasche, C., Vaccarella, S., Barzan, L., Franceschi, S. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control 13 (2002) 957-964

Tankere, F., Camproux, A., Barry, B., Guedon, C., Depondt, J., Gehanno, P. Prognostic value of lymph node involvement in oral cancers: a study of 137 cases. Laryngoscope 110 (2000) 2061-2065

Therneau, T., Gambusch, P. (2015) A package for survival analysis in S (http://cran.r-project.org/web/packages/survival) Access Date: 17.03.2017

Union for International Cancer Control (UICC) (2016) TNM Classification of Malignant Tumours - 8th edition: Changes between the 7th and 8th editions (http://www.uicc.org/resources/tnm/publications-resources) Access Date: 21.03.2017

Walker, D.M., Boey, G., McDonald, L.A. The pathology of oral cancer. Pathology 35 (2003) 376-383

Wittekind, C., Asamura, H., Sobin, L.H. Head and neck tumors. (2015) In: "TNM Atlas - Illustrated Guide to the TNM Classification of Malignant Tumours", Wittekind C, Asamura H, Sobin LH (eds), UICC and John Wiley & Sons, Ltd John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK, 2015, pp 1-71

Witten, J., Hybert, F., Hansen, H.S. Treatment of malignant tumors in the parotid glands. Cancer 65 (1990) 2515-2520

Wolff, K.D., Bootz, F., Beck, J., Bikowski, K., Böhme, P., Budach, W., Burkhardt, A., Danker, H., Eberhardt, W., Engers, K., Fietkau, R., Frerich, B., Gauler, T., Germann, G., Gittler- Hebestreit, N., Grötz, K., Horch, R., Ihrler, S., Keilholz, U., Lell, M., Lübbe, A., Mantey, W., Nusser-Müller-Busch, R., Pistner, H., Paradies, K., Reichert, T., Reinert, S., Schliephake, H., Schmitter, M., Singer, S., Westhofen, M., Wirz, S., Wittlinger, M. (2012a) S3-Leitlinie "Diagnostik und Therapie des Mundhöhlenkarzinoms". In: Deutsche Gesellschaft für Mund-Kiefer- und Gesichtschirurgie (ed) Registernummer 007 - 100OL, Klassifikation S3. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF) Stand: 16.11.2012, gültig bis 31.12.2015, p 119

Wolff, K.D., Follmann, M., Nast, A. The diagnosis and treatment of oral cavity cancer. Deutsches Arzteblatt international 109 (2012b) 829-835

Wolff, K.D., Hölzle, F. "Raising of Microvascular Flaps: A Systematic Approach“, 2nd Edition, Springer, Berlin, 2011

Woolgar, J.A., Triantafyllou, A., Lewis, J.S., Jr., Hunt, J., Williams, M.D., Takes, R.P., Thompson, L.D., Slootweg, P.J., Devaney, K.O., Ferlito, A. Prognostic biological features in neck dissection specimens. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 270 (2013) 1581-1592

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Appendix

Original research article 1: “Elective neck dissection in salivary gland carcinomas—yes or no?”

Head and Neck Salivary Gland Carcinomas—Elective Neck Dissection, Yes or No?

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Purpose: Surgical resection and subsequent neck dissection (ND) in cases of clinically positive lymph nodes is an accepted primary treatment strategy for salivary gland carcinomas. Because of uncertainty in the extent of lymphogenic metastasis, the authors advocate a strategy of surgical resection and elective ND (END) for all patients. The authors evaluated their treatment by estimating the frequency of metastatic disease and identifying factors associated with an increased risk for metastatic disease.

Materials and Methods: A retrospective cohort study was implemented using patient data obtained from the university's interdisciplinary board for head and neck tumors. Data were screened for age, gender, tumor entity, localization, grade, and TNM Classification of Malignant Tumors (by UICC, International Union Against Cancer) status. Statistical analysis was performed to identify possible predictors of lymph node metastasis. Nodal status groups (N^+ and N0) were compared with respect to age by *t* tests; other comparisons involved χ^2 tests.

Results: Ninety-four patients (50% female, 50% male; mean age, 59.12 yr) were identified, of whom 87 had an indication for END. On postsurgical histopathologic examination, 34 (39%; 17 male, 17 female) were diagnosed with N^+. Statistical analysis for nodal status produced explorative *P* values (age, $P = .001$; gender, $P = .792$; anatomic region, $P = .114$; tumor entity, $P = .854$; tumor status, $P = .263$; grade, $P = .000$).

Conclusion: All studied malignancies were capable of lymph node dissemination. Therefore, no reliable preoperative predictors for lymphogenic metastasis are currently identifiable. Because of difficulties in safely predicting lymphogenic metastasis and the high rate of N^+ results on postoperative examination, the authors strongly advise END for all patients with salivary gland carcinoma.

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Salivary gland carcinomas occur with an incidence of 1.1 in 100,000 per year in Caucasian populations[1,2] and constitute about 5% of all head and neck carcinomas.[3] Salivary gland malignancies represent a heterogeneous group of neoplasms, with 24 different types recognized by the World Health Organization.[4]

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The most frequently encountered subtypes are adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and acinic cell carcinoma.[1,2] Because of the rareness and diversity of these tumors, the choice of an appropriate treatment strategy is challenging.[3] The current literature lacks studies featuring larger groups of patients or data on differences in the behavior of minor versus major salivary gland malignancies. Therefore, evidence-based surgical guidelines of treatment are not yet possible, especially not for treating subtypes. In consequence, a controversial debate exists concerning the various treatment strategies, such as neck dissection (ND) as an elective procedure in all patients versus ND only in patients with cN1.

Surgical resection of the malignancy is widely accepted as a primary form of treatment, although the extent of the surgical procedure is disputed.[5,6] ND is often recommended in cases of clinical neck disease by most researchers, regardless of histology or site,[3,7] but management of the clinical N0 neck remains unclear.[7,8] Postoperative radiotherapy is usually preferred in cases of adverse prognostic factors based on pathology, such as a high grade, positive surgical margins, or lymph node metastasis.[9] Therefore, radiation therapy is often omitted from the initial surgical treatment so that it can be used as a future option if sampled lymph nodes from the ND prove positive.[7,10] Multimodal concepts also are controversial; chemotherapeutic approaches with molecularly targeted agents and postoperative radiation therapy might help to improve therapeutic outcomes,[11] although their application is variable. For chemotherapy, no benefit has been shown thus far in induction or adjuvant therapy. Some investigators have advocated the use of chemotherapeutic agents in patients under palliative care or in those with advanced, unresectable, or metastatic disease,[3,12] but no convincing data support the routine use of other cytotoxic, hormonal, or targeted agents.[13] Response rates to chemotherapy are low and response duration is generally short-lived; therefore, based on the available data, no standard chemotherapy regime can be recommended.[14] One reason for this debate might be the lack of consistent data concerning the rate of cervical metastasis,[3] possibly because of individual studies reporting rates as high as 53%.[15] Nevertheless, consensus has been reached on the predictors for a high probability of occult metastasis, namely unfavorable histology, pathologic grade, and the stage and size of the primary lesion.[16]

Furthermore, some recommendations for the treatment of salivary gland carcinomas are based on data obtained from experience with squamous cell carcinoma of the head and neck region. Therefore, doubt remains as to whether some of these treatments actually improve patient survival, because no evidence exists showing the similar behavior of these 2 kinds of malignancy.[7] In consequence, research concerning the treatment of the various salivary gland carcinomas must be extended, but because of their rareness and diversity, any single institution might find it difficult to amass a sufficient number of affected patients, making the achievement of significant results leading to evidence-based clinical guidelines of treatment extremely difficult. The authors hope to contribute to this search for suitable guidelines and to share, in this study, their clinical experience and research relating to salivary malignancies.[17]

The purpose of this study was to shed light on cervical lymph node involvement in salivary gland carcinoma and to provide recommendations for neck management.

The authors hypothesized that the optimal strategy of treatment to address the risk of lymph node metastasis in patients with salivary gland carcinoma would consist of surgical removal of the primary tumor lesion followed by elective ND (END). The specific aim of the study was to validate this procedure by an evaluation of the postoperative histopathologic lymph node results of patients. Therefore, the authors retrospectively retrieved data on the age, gender, TNM Classification of Malignant Tumors (by UICC, International Union Against Cancer) status, grade, tumor entity, and tumor location of patients with salivary gland carcinoma. These variables were analyzed by postoperative nodal status to possibly determine the groups that had benefited from END and the groups in which it could have been omitted.

Materials and Methods

STUDY DESIGN

To address the research purpose, a retrospective cohort study was designed and implemented to analyze the histopathologic data of affected patients.

STUDY SAMPLE

The study population was composed of patients presenting at the authors' university teaching hospital for the evaluation and management of salivary gland malignancies from October 2006 through October 2012. To be included in the study, patients had to be diagnosed with malignant salivary gland carcinomas and not to have been treated with ND or radiotherapy. All cases were presented to the authors' interdisciplinary board for head and neck cancers. After interdisciplinary board discussion, primary tumor surgery and subsequent ND were performed in all possible cases, in clinically negative cases, and in clinically positive cases. Standard procedure featured preoperative imaging followed by surgical resection of the primary tumor lesion

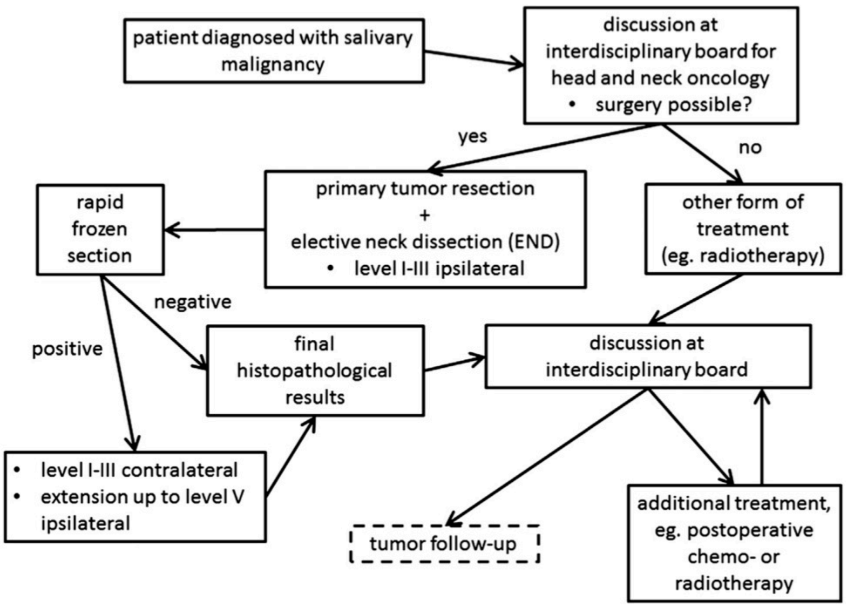

FIGURE 1. Treatment algorithim and surgical procedure.

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with sufficient safety margins and ipsilateral ND from levels I to III. If rapidly frozen sections showed positive lymph node results in levels II and III, surgery was extended up to level V ipsilaterally and levels I to III contralaterally (Fig 1). Contralateral ND was omitted in cases with positive frozen sections from primary tumors of the parotid or submandibular gland, because of generally infrequent contralateral metastasis. Instead, these patients received tumor follow-up, consisting of computed tomographic scans every 6 months during the first 2 years and 1 scan per year for the next 5 years. ND as a whole was omitted only for reasons such as a poor overall health status that did not allow surgical and anesthetic interventions, very advanced age, or patients declining to give consent for surgery. Radiotherapy was performed only as postoperative therapy. It was usually carried out as an additional form of treatment after a second interdisciplinary board discussion of cases with positive lymph node results in the final histopathologic findings.

DATA COLLECTION METHODS

Patient data were obtained retrospectively after therapy from the university's interdisciplinary board for head and neck tumors. Medical records were screened for clinical data and the final histopathologic findings were obtained for evaluation.

VARIABLES

Patient data were screened for patient age, gender, ND results, tumor entity, tumor location, grade, and tumor status, whenever accessible. Then, these predictor variables were analyzed to determine whether any had a significant influence on the outcome of postoperative lymph node status.

DATA ANALYSIS

The analysis of data was approved by the local ethics committee (registration number 2777/10) and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent. Statistical analysis was performed to identify predictors of lymph node metastasis. The 2 nodal status groups were compared with respect to age using the *t* test for 2 independent samples. Comparisons with respect to gender, tumor location, tumor entity, anatomic region, grade, and tumor stage were carried out by χ^2 tests with 1, 3, 4, 6, and 7 degrees of freedom, respectively. Explorative *P* values were 2-sided, and SPSS 19.0.0 (IBM SPSS, Inc, Chicago, IL) was used for statistical calculations. Statistical analysis was performed by Prof Dr Wagenpfeil.

Results

Data of 94 patients were reviewed; 47 were women (50%) and 47 were men (50%). Patients' mean age was 59.1 years (standard deviation, 16.5 yr; median, 66 yr; range, 11 to 89 yr). Eighty-seven patients (92.6%) were treated by ND, whereas 7 patients (7.4%) were not.

In the histopathologic findings of removed lymph nodes, 53 cases (60.9%) showed tumor-free nodes and 34 (39.1%) showed metastasis. Of these 34 patients, 16 were men (39.6%) and 18 were women (42.9%).

Forty-one malignancies (43.6%) arose from the parotid gland, 15 (16.0%) from the submandibular gland, and 16 (17.0%) from minor salivary glands of the palate; 22 (23.4%) carcinomas had developed in the other minor salivary glands of the oral cavity. Thirty patients (31.9%) were diagnosed with mucoepidermoid carcinoma, which therefore was the malignancy that was observed most frequently; 22 (23.4%) had adenocarcinoma, 19 (20.2%) had adenoid cystic carcinoma, 7 (7.4%) had acinic cell carcinoma, and 16 (17.0%) had other, less common, salivary malignancies.

In relation to gender and nodal status, 17 male (50.0%) and 17 female (50.0%) patients were diagnosed with pN1 from the postoperative lymph node results.

With regard to location, 14 cases (41.2%) with positive lymph nodes had the primary tumor in the parotid gland, 7 (20.6%) in the submandibular gland, 2 (5.9%) in minor salivary glands of the palate, and 11 (32.4%) in minor glands of the remaining oral cavity. In relation to tumor entity, mucoepidermoid carcinoma yielded 12 cases (35.3%) of positive lymph nodes, adenocarcinoma 8 cases (23.5%), adenoid cystic carcinoma 7 cases (20.6%), acinic cell carcinoma 1 case (2.9%), and other entities 6 cases (17.6%).

Of patients with positive lymph nodes, 12 (35.3%) had T1, 11 (32.4%) had T2, 8 (23.5%) had T3, and 3 (8.8%) had T4. In relation to tumor grade, 3 (10.0%) were G1, 7 (23.3%) were G2, 1 (3.3%) was G2 to G3, 18 (60.0%) were G3, and 1 (3.3%) was G4.

Explorative *P* values in relation to nodal status were .001 for age, .792 for gender, .114 for anatomic region, .854 for tumor entity, .263 for tumor status, and .000 for tumor grade (Table 1).

Eleven patients were diagnosed with G1 mucoepidermoid carcinoma, and none showed lymph node metastasis in the final histopathologic examination.

Discussion

The authors advocate a strategy of surgical resection and END for all cases of salivary gland carcinoma, not only clinically positive cases. By this method, the authors hope to address the uncertainty in the extent and presumably high risk of occult lymph node metastasis in affected patients. The purpose of this study was to evaluate this specific treatment by estimating the frequency of metastatic disease and by identifying factors associated with an increased risk for metastatic disease. From this, the authors hoped to pinpoint the groups that might benefit from END and the groups for which this method could be omitted. In this retrospective study of data from patients treated at the authors' university hospital from 2006 through 2012, the authors aimed to facilitate decisions in favor or against the surgical treatment of ND therapy and to contribute to the development of specific guidelines. After a review of the retrospective study data with regard to lymph node metastasis, 39.5% of the present patients had positive lymph node results, and no group was identified that showed that this surgical method was expendable. All tumor entities showed a capacity for lymphogenic metastasis.

The results show the difficulty of estimating the risk for occult metastasis in the clinical preoperative setting. Although grade (P = .000) and advanced age (P = .001) exhibited a relation to an elevated risk, these 2 factors were not sufficient to serve as safe predictors in the preoperative setting. The occurrence of occult metastasis in even low-grade and small tumors (>30% of patients with positive findings graded G2 or lower) makes these variables too weak to serve as a basis for a decision in favor or against END. Therefore, the authors strongly advocate routine ND in all patients diagnosed with salivary malignancies.

Arrival at the optimal treatment strategy for salivary gland cancer remains a challenge for all involved medical disciplines, particularly because of the rareness of this cancer and the diverse range of tumor entities. The low frequency of patients makes it especially difficult to acquire a sufficient number of relevant patients in an acceptable period. Therefore, specific guidelines for treatment have, unsurprisingly, not been established. In particular, the benefit of END to seek out occult lymph node metastasis in these patients remains controversial.

END is usually performed after the removal of the primary lesion in the same operative session. As a prophylactic measure against occult lymph node metastasis, this permits the future treatment option of radiation therapy. Radiotherapy can be used secondarily as an effective further treatment in cases of lymph node metastasis, thereby avoiding the risk and additional morbidity of a second surgical intervention. The possibility of metastasis can be estimated based on predictors, such as advanced age, histology, pathologic grade, and stage or size of the primary lesion,[16-20] as shown in the present results; however, because of the wide, diverse range of tumor entities, a high risk for patients remains. Thus, the often curative intent of surgical tumor lesion removal might be threatened by possible metastasis, if ND is omitted. Therefore, the identification and differentiation of groups of patients in whom END can be omitted and in whom it cannot are vital. This decision is often made according to the patient's preoperative lymph node status. A limitation of END only to patients with cN^+ lymph nodes in the preoperative staging could be risky. The diagnosis of cN stage is based on various criteria and staging methods (eg, magnetic resonance

Table 1. PATIENT DEMOGRAPHICS

	Total (n = 87)		ND Positive (n = 34)		ND Negative (n = 53)		
Characteristics	n	%	n	%	n	%	Explorative *P* Value
Age (yr), mean ± SD	58.43 ± 16.820		65.21 ± 14.047		54.08 ± 17.127		.001
Gender							.792
Male	45	51.7	17	50.0	28	52.8	
Female	42	48.3	17	50.0	25	47.2	
Anatomic							.114
Parotid gland	38	43.7	14	41.2	24	45.3	
Submandibular gland	14	16.1	7	20.6	7	13.2	
Minor salivary glands, palate	14	26.1	2	5.9	12	22.6	
Other minor salivary glands, cavum oris	21	24.1	11	32.4	10	18.9	
Histopathologic							.854
Mucoepidermoid carcinoma	30	34.5	12	35.3	18	34.0	
Adenocarcinoma	21	24.1	8	23.5	13	24.5	
Adenoid cystic carcinoma	16	18.4	7	20.6	9	17.0	
Acinic cell carcinoma	6	6.9	1	2.9	5	9.4	
Other carcinomas	14	16.1	6	17.6	8	15.1	
Tumor status (n)	81		34		47		.263
T1	35	43.2	12	35.3	23	48.9	
T2	25	30.9	11	32.4	14	29.8	
T3	12	14.8	8	23.5	4	8.5	
T4	9	11.1	3	8.8	6	12.8	
Grade (n)	65		30		35		.000
G1	24	36.9	3	10.0	21	60.0	
G2	15	23.1	7	23.3	8	22.9	
G2-3	1	1.5	1	3.3	0	0	
G3	24	36.9	18	60.0	6	17.1	
G4	1	1.5	1	3.3	0	0	

Abbreviations: ND, neck dissection; SD, standard deviation.

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imaging, computed tomography, sonography, clinical examination) that do not have the same sensitivity and specificity. Therefore, the authors perform END in all possible cases to counter the risk of occult metastasis. In the present study of 94 patients, ND was omitted in only 7 cases because of contraindications (eg, poor overall health status, very advanced age, patients declining to give consent). Another issue is the entity of low-grade mucoepidermoid carcinomas. These have a relatively low risk of lymph node metastasis, and the necessity of END for this subtype should be discussed. In the authors' opinion, END can be omitted only in this group, if all radiologic and clinical diagnostics most strongly indicate a clinically negative neck and if findings from preoperative biopsies are conclusive for low-grade mucoepidermoid carcinoma. Unfortunately, in the daily clinical setting, this is not possible for all cases, and uncertainties will always remain, so that reliance has to be placed on the knowledge and experience of the tumor surgeon. Of the present 94 patients, 11 were diagnosed as having low-grade mucoepidermoid carcinoma by postoperative histopathologic examination. None of them had positive lymph node results. In these cases, END might have been omitted from a retrospective point of view, but the perioperative setting is not always clear. If there is any doubt, the authors always recommend END.

This recommendation also applies for the relation of the primary tumor location to the risk for lymph node metastasis. In this study, for example, of 14 cases of minor salivary gland tumors in the palate, only 2 showed nodal involvement, whereas 7 of 14 submandibular gland tumors showed such involvement. Although the results indicate different risks for nodal metastasis in certain locations, the results are not significant enough to provide straight recommendations. Once again, the experienced clinician is left to make his decision concerning END and, in cases in which the risk for nodal neck involvement has been assessed to be extremely low, to omit this method. In general, the authors always recommend END, because it is a safe and effective way to counter tumor recurrence.

The present results were compared with those of other studies. In 407 patients with clinically negative necks, Armstrong et al,[19] observed that occult disease occurred in 38% (ie, 34 of 90 cases; END in 22%, 90 of 407 cases) in whom END was performed, showing similar results to the present study. Because ND follows the primary tumor resection in a single operation, additional morbidity is low. Similar observations for major salivary gland carcinomas have been reported by Zbaren et al[21] who advocated ND for every patient, because of the marked uncertainties in predicting occult lymph node metastasis. Stennert et al[15] recommended ND in major salivary gland cancers, because even the incidence rates of so-called low-risk tumors are observed at values of 22% to 47%. One of the first studies observing the occasionally aggressive local growth and distant metastasis of tumors, which might even be considered benign by some pathologists, was undertaken by Spiro et al.[22]

In a systematic review carried out by Valstar et al,[8] the pooling of available data from suitable articles showed that in 32 of 137 ENDs (weighted average, 23%; range, 20-30%), positive nodes were present. These figures indicate that a substantial number of occult metastases occur in patients, and that elective treatment by ND or radiotherapy is recommended. After this kind of procedure, regional recurrences are reported in only 5% of patients, thereby stressing its effectiveness.

One benefit of the present study is that it features a relatively large number of patients treated in a realistic clinical setting. Unfortunately, this number is still not sufficient to limit the population to a specific regional or histologic group, thus leaving uncertainty in the handling of specific subtype groups in which certain predictions cannot be made. This could be a goal for future studies to enable recommendations for treating subtypes. The authors' aim was to provide general advice on the surgical management of salivary gland carcinoma in the hope of aiding the clinician in making and facilitating decisions.

On the whole, salivary malignancy is a particularly challenging disease, not only because of its rareness, but also because of the lack of well-founded clinical treatment guidelines. Therefore, the collection and release of further relevant data acquired by future studies is vital, especially for achieving recommendations on treating subtypes. Because of the overall high rates of occult lymph node metastasis and the lack of reliability in predicting this spread, END seems highly favorable. The commonly practiced strategy of primary resection and immediate ND adds only a minimal increase to patient morbidity. The present research has shown that this method is an important tool for the surgical treatment of all patients with salivary gland carcinoma, and that its omission might lead to a high risk of failure to counter lymph node metastasis at an early stage and, hence, improve patient survival.

References

1. Bjorndal K, Krogdahl A, Therkildsen MH, et al: Salivary gland carcinoma in Denmark 1990-2005: Outcome and prognostic factors. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 48:179, 2012
2. Bjorndal K, Krogdahl A, Therkildsen MH, et al: Salivary gland carcinoma in Denmark 1990-2005: A national study of incidence, site and histology. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncol 47:677, 2011
3. Bell RB, Dierks EJ, Homer L, et al: Management and outcome of patients with malignant salivary gland tumors. J Oral Maxillofac Surg 63:917, 2005
4. Eveson JW, Auclair PL, Gnepp DR, et al: World Health Organization classification of tumours: Pathology & genetics. Head and neck tumours. 2005, *in* Tumors of the Salivary Glands [Internet]. Lyon, France: IARC Press, 2005, p 212–215. Available at: http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb9/bb9-chap5.pdf
5. Witten J, Hybert F, Hansen HS: Treatment of malignant tumors in the parotid glands. Cancer 65:2515, 1990
6. Alajmo E, Polli G, De Meester W: Total parotidectomy—A routine treatment for parotid gland swellings? J Laryngol Otol 103:181, 1989
7. Gold DR, Annino DJ Jr: Management of the neck in salivary gland carcinoma. Otolaryngol Clin North Am 38:99, 2005
8. Valstar MH, van den Brekel MW, Smeele LE: Interpretation of treatment outcome in the clinically node-negative neck in primary parotid carcinoma: A systematic review of the literature. Head Neck 32:1402, 2010
9. Andry G, Hamoir M, Locati LD, et al: Management of salivary gland tumors. Expert Rev Anticancer Ther 12:1161, 2012
10. Jackson GL: Management of the neck in parotid cancer. Am J Surg 177:278, 1999
11. Surakanti SG, Agulnik M: Salivary gland malignancies: The role for chemotherapy and molecular targeted agents. Semin Oncol 35:309, 2008
12. Debaere D, Vander Poorten V, Nuyts S, et al: Cyclophosphamide, doxorubicin, and cisplatin in advanced salivary gland cancer. B-ENT 7:1, 2011
13. Laurie SA, Ho AL, Fury MG, et al: Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: A systematic review. Lancet Oncol 12:815, 2011
14. Papaspyrou G, Hoch S, Rinaldo A, et al: Chemotherapy and targeted therapy in adenoid cystic carcinoma of the head and neck: A review. Head Neck 33:905, 2011
15. Stennert E, Kisner D, Jungehuelsing M, et al: High incidence of lymph node metastasis in major salivary gland cancer. Arch Otolaryngol Head Neck Surg 129:720, 2003
16. Kelley DJ, Spiro RH: Management of the neck in parotid carcinoma. Am J Surg 172:695, 1996
17. Dodson TB: A guide for preparing a patient-oriented research manuscript. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104:307, 2007
18. Kokemueller H, Brueggemann N, Swennen G, et al: Mucoepidermoid carcinoma of the salivary glands—Clinical review of 42 cases. Oral Oncol 41:3, 2005
19. Armstrong JG, Harrison LB, Thaler HT, et al: The indications for elective treatment of the neck in cancer of the major salivary glands. Cancer 69:615, 1992
20. Frankenthaler RA, Luna MA, Lee SS, et al: Prognostic variables in parotid gland cancer. Arch Otolaryngol Head Neck Surg 117:1251, 1991
21. Zbaren P, Schupbach J, Nuyens M, et al: Elective neck dissection versus observation in primary parotid carcinoma. Otolaryngol Head Neck Surg 132:387, 2005
22. Spiro RH, Huvos AG, Berk R, et al: Mucoepidermoid carcinoma of salivary gland origin. A clinicopathologic study of 367 cases. Am J Surg 136:461, 1978

Original research article 2: “Elective neck dissection in unilateral carcinomas of the tongue - unilateral vs. bilateral approach”

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Elective neck dissection in unilateral carcinomas of the tongue: Unilateral versus bilateral approach

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A B S T R A C T

Purpose: Elective neck dissection (END) is a common primary treatment strategy for oral tongue squamous cell carcinoma (OTSCC), although uncertainty remains regarding the necessary extent of END for strictly unilateral early stage OTSCC. The authors evaluated two END variations, unilateral and bilateral, to determine the optimal extent.
Materials and methods: A retrospective cohort study was performed on patient data from two departments of oral and maxillofacial surgery. All previously untreated patients from both clinics who were diagnosed with early-stage (pT1-2) unilateral OTSCC were included. The following variables were collected: age, gender, END type/extent, tumor localization, later nodal metastasis, and TNM status. Statistical analyses were performed ($p < 0.05$).
Results: A total of 150 patients were identified, 105 receiving unilateral END and 45 bilateral END. The rates of postoperative positive lymph nodes were 21.9% for ipsilateral END and 26.7% for bilateral END (bilateral END: all positive nodes ipsilateral). In all, 14 patients in the ipsilateral group developed nodal metastasis during tumor aftercare (11 patients ipsilateral, 3 patients contralateral neck). In the bilateral group, nodal metastasis was later observed in 4 cases (8.9%; 3 cases ipsilateral, 1 case contralateral neck). Statistical analysis could not detect significant differences between the END procedures.
Conclusion: As both procedures lead to similar results in preventing or omitting possible later nodal metastasis, the two methods seem to be valuable alternatives. In conclusion, we recommend bilateral END because of advantages with regard to oncologic safety and esthetic outcome, but the decision for END should always be according to the patient's general health status, comorbidities, and individual tumor risk profile.

1. Introduction

The tongue is the most frequent location with regard to oral cancer (Moore et al., 2000). In general, malignancies of the oral cavity are the seventh most common tumors in German males. Incidence rates of 17.9 per 100,000 for males and 6.0 per 100,000 for females in Germany make it a serious health threat (Robert Koch Institut, 2015). Concerning the tongue, the estimated male incidence rates per year show a large amount of variation, e.g., from 9.4 in India to 1.1 in the UK (Moore et al., 2000; Prince and Bailey, 1999). Over 95% of these malignancies are squamous cell carcinomas, associated with the classic risk factors of alcohol and tobacco, and a

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combination of these two factors seems to multiply the tumor development risk (Talamini et al., 2002). At the molecular level, an overexpression of vascular endothelial growth factor (VEGF) and its isoforms (Aggarwal et al., 2014; Kyzas et al., 2005) and of VEGF receptors (Pianka et al., 2015) is commonly observed in oral squamous cell carcinomas (OSCC). Primary treatment of oral tongue squamous cell carcinomas (OTSCC) usually involves resection of the tumor lesion (Wolff et al., 2012). To address, in oral cancer, the high rates of occult metastasis, which show a high amount of variation throughout the literature with ranges of up to 34% (Dogan et al., 2014; Shah et al., 1990), subsequent neck dissection to a variable extent is performed according to the patient's estimated risk profile. Therefore, an elective neck dissection of the ipsilateral levels I–III in all affected patients is recommended as oral cavity carcinoma treatment (Wolff et al., 2012). Based on the final histopathological findings, recommendations for postoperative therapy can be given. These can include radiotherapy or, in cases of extracapsular lymph nodes, a combination of radio- and chemotherapy. Although many advances regarding operative and postoperative treatment have been made during the past few decades, the absolute 5-year survival rate in Germany averages about 50% (males: 43%; females: 55%) (Robert Koch Institut, 2015). This poor rate is mainly caused by metastatic disease at regional or distant sites and by local recurrence (Sano and Myers, 2007; Yuen et al., 1997). The literature is consistent in showing that the most reliable prognostic factor in OTSCC is the presence of cervical metastasis in the lymph nodes (Grandi et al., 1985; Sano and Myers, 2007; Schuller et al., 1980). Because of the above-mentioned poor survival rates, the effective treatment of OTSCC remains challenging. In consequence, a sensible approach is to limit its treatment to specialized cancer centers only.

In the literature, the question of the use of elective neck dissection (END) in carcinomas of the oral tongue and especially with regard to the extent of END (De Zinis et al., 2006; Huang et al., 2008; Khafif et al., 2001; Silver and Moisa, 1991) remains open. A decision is often made according to clinical nodal status (cN+/−) or T-stage (T1–4). As mentioned above, for carcinomas of the oral cavity in general, END is recommended at least for the ipsilateral levels I–III (according to Robbins et al., 2002) in all patient cases, irrespective of the pre-interventional cN status (Wolff et al., 2012). A bilateral END approach for tongue carcinomas is sometimes favored in more advanced primary tumors, e.g., T3–4 tumors that cross the tongue's midline or in patients with initially positive lymph node metastasis (Koo et al., 2006; Lim and Choi, 2007; Lim et al., 2006). The literature still lacks concise recommendations concerning this issue of the extent of END in unilateral tongue carcinomas. Depending on the opinions and routines of the department carrying out the treatment, the neck dissection protocol for these patients usually ranges from the removal of ipsilateral levels I–III to the removal of both bilateral levels I–III.

The purpose of this study has been to clarify the remaining questions concerning the optimal extent of END treatment in patients with unilateral OTSCC. Another aim of this study has been to retrospectively analyze patient data from two hospitals, in both of which oral and maxillofacial surgery is undertaken, in order to help to identify the ideal level of END extension.

2. Material and methods

2.1. Study design

To address the raised questions regarding the benefit and optimal extent of END in patients with unilateral OTSCC, a retrospective cohort study was designed.

2.2. Study sample

The study sample consists of two different cohorts of OTSCC patients, distinguished from each other in the form of END treatment received. To be included in the general study population, patients had to be diagnosed with T1–2 OTSCC. The primary tumor lesion had to be limited to only one side of the tongue (e.g., right or left side) and was not allowed to cross the midline of the tongue. In the first contributing department (Department of Oral and Maxillofacial Surgery of the Technische Universität Munich [TUM]), all included patients presented for treatment of unilateral OTSCC between December 2006 and July 2015, and in the second contributing department (Department of Oral and Maxillofacial Surgery of the Ludwig-Maximilians-Universität Munich [LMU]), the included patients were treated between February 2007 and April 2015.

In the first department (TUM), the preferred treatment strategy consisted of surgical removal of the primary tumor lesion and ipsilateral neck dissection, extending from levels I–III. In the other department (LMU), the preferred END treatment protocol, in contrast, favored bilateral removal of levels I–III. In the department performing ipsilateral END, intraoperative rapidly frozen sections were taken from all patients for pathological examination. If tumor-positive lymph nodes were found, neck dissection was immediately extended to the ipsilateral levels IV–V and to the contralateral levels I–III. Tumor aftercare usually featured continuous clinical controls every 3–6 months and a computed tomography scan each year.

2.3. Data collection methods

The data from the universities' interdisciplinary boards for head and neck tumors were screened retrospectively for patients with matching criteria. Additional relevant clinical data of indexed patients were then retrieved via the universities' clinical file management system at both institutions.

2.4. Variables

General patient data were screened for information such as age, gender, preoperative staging results, surgical reports, histopathological findings (e.g., TNM stage), interdisciplinary tumor board recommendations, and postoperative treatment procedures.

2.5. Data analysis and statistical calculations

The collection and analysis of the study's data was approved by the university's local ethics committee (registration numbers 2777/10 and 383/15). The research was conducted in accordance with the Declaration of Helsinki. The patient data from both participating institutes were combined, and statistical analysis was performed to obtain information on the rate of positive lymph nodes in the END and on later nodal metastasis during follow-up. Possible predictors of the rate of occult or future lymph node metastasis (e.g., gender, age) were sought. SPSS 22.0.0 software (IBM SPSS, Inc., Chicago, IL, USA) was used for statistical calculations. Descriptive and inferential statistics were computed by using the two-sample t test, chi-squared test, or Fisher exact test. Recurrence-free survival was assessed by using the Kaplan–Meier estimator. Differences between ipsilateral and bilateral neck dissections with regard to recurrence-free survival were examined by using Cox proportional hazard models. All analyses were conducted by using the survival-package in R version 3.2.4 (R-Core-Team; Therneau and Gambusch). A p value of less than 0.05 was considered to be statistically significant.

3. Results

Altogether, the study reviewed and analyzed the data of 150 patients who had been diagnosed with unilateral OTSCC and had not received any previous treatment (Table 1, Fig. 1). Of the patients, 83 were male (55.3%) and 67 were female (44.7%). The mean age of the patients was 59.3 years (median: 60 years, standard deviation [SD]: 14.5), with ages ranging from 19 to 86 years. The primary tumor lesion was located on the left side in 75 cases (50.7%) and on the right side in 73 cases (49.3%). Regarding the surgical procedure of the general study population, 105 patients (70%) received ipsilateral END from levels I–III (57 left, 54.3%; 48 right, 45.7%) and 45 patients (30%) were treated with bilateral END. Later nodal metastasis was observed in 18 patients (12%): in 14 cases (9.3%) on the ipsilateral neck, and in 4 cases (2.7%) on the contralateral neck. The mean time until delayed nodal metastasis was 21.6 months (range: 4–79 months; median: 11.5 months) (Fig. 2, Table 2). On postoperative histopathological examination, 115 patients (76.7%) showed no signs of lymph node infiltration (pN−) and 35 patients (23.3%) showed positive lymph node infiltration (pN+). With regard to TNM classification (International Union Against Cancer [UICC]), 105 patients (70.5%) had a T1 tumor and 44 patients (29.5%) had a T2 tumor. Tumor grading was distributed as follows: 29 (20.4%) patients, G1; 1 (0.7%) patient, G1–2; 87 (61.3%) patients, G2; 4 (2.8%) patients, G2–3; and 21 (14.8%) patients, G3. The total number of 150 included patients was divided into two study groups A and B, according to their surgical treatment protocol (Fig. 1).

The population of study group A consisted of 105 patients (70%), all of whom were treated with unilateral END of levels I–III; 63 patients (60%) of this group were male and 42 patients (40%) were female, with a mean age of 60.9 years (median: 61 years, SD: 14.6, range 19–86 years). The OTSCC originated, in 58 cases (55.2%), from the left side of the tongue and, in 47 cases (44.8%), from the right side of the tongue. Of the 105 treated patients in group A, 91 (86.7%) remained tumor-free until the end of the study (July 2015). Delayed cervical nodal metastases were observed in 14 patients (13.3%) (Table 3). In 11 of these cases, the nodal metastasis was on the same side as the primary lesion (10.5%) and, in 3 cases, on the contralateral side (2.9%). The mean time until delayed nodal metastasis of the 14 affected patients in group A was 18.43 months (range: 4–79 months; median: 11.5 months).

A total of 77 patients (73.3%) were released into tumor follow-up and were not recommended adjuvant treatment. A total of 23 patients (21.9%) were advised to undergo adjuvant radiotherapy (RTx), 4 patients (3.8%) combined radio- and chemotherapy (RCTx), and 1 patient (1.0%) adjuvant chemotherapy (CTx).

All 105 patients in group A received ipsilateral END from levels I–III. In 57 patients (54.3%), END was performed on the left side of the neck, and in 48 patients (45.7%), on the right side of the neck. During all surgical interventions, rapid-frozen sections were taken and sent for direct histopathological examination. If the results showed signs of malignancies, the neck dissection was extended to levels IV and V on the ipsilateral side and to levels I–III on the contralateral side. Out of the 105 treated patients, 92 (93.9%) had tumor-free rapid-frozen sections and 6 patients (6.1%) tumor-positive sections. After completion of the surgical intervention, the tumor and neck dissection specimens were sent for detailed histopathological diagnostics. In the final results, 82 patients (78.1%) did not show signs of lymph node infiltration (pN−), and 23 patients (21.9%) did show positive lymph nodes (pN+). Concerning TNM classification, 75 patients (72.1%) had a tumor classified as T1 and 29 patients (27.9%) had a tumor classified as T2. With respect to tumor grading, 22 (22.4%) were graded as G1, 1 (1%) as G1–2, 63 (64.3%) as G2, 4 (4.1%) as G2–3, and 8 (8.2%) as G3. With regard to lymph node status and nodal metastasis subsequently in the course of the disease, 4 patients with later nodal metastasis were found to be pN+ (28.6%) and 10 patients pN− (71.4%) with regard to the postoperative histopathological findings. Out of the 14 patients with later nodal metastasis (13.3%), 7 patients (50%) had a T1 and 7 patients (50%) a T2 primary tumor. The tumor grading in the 14 later nodal metastasis patients was as follows: 2 patients (14.3%) were classified as G1, 10 patients (71.4%) as G2, 1 patient (7.1%) as

Table 1
Patient characteristics.

	Overall (N = 150)	Ipsilateral END (n = 105)	Bilateral END (n = 45)	p-Value
Age [mean ± SD]	59.3 ± 14.5	60.9 ± 14.6	55.6 ± 13.9	0.044
Sex [n (%)]				
Male	83 (55.3%)	63 (60.0%)	20 (44.4%)	0.115
Female	67 (44.7%)	42 (40.0%)	25 (55.6%)	
Later nodal metastasis [n (%)]				
None	132 (88.0%)	91 (86.7%)	41 (91.1%)	0.814
Ipsilateral	14 (9.3%)	11 (10.5%)	3 (6.7%)	
Contralateral	4 (2.7%)	3 (2.8%)	1 (2.2%)	
Adjuvant therapy [n (%)]				
None	111 (74.0%)	77 (73.3%)	34 (75.6%)	0.200
RTx	29 (19.3%)	23 (21.9%)	6 (13.3%)	
RCTx	9 (6.0%)	4 (3.8%)	5 (11.1%)	
CTx	1 (0.7%)	1 (1.0%)	0 (0.0%)	
Nodal status [n (%)]				
pN+	35 (23.3%)	23 (21.9%)	12 (26.7%)	0.674
pN−	115 (76.7%)	82 (78.1%)	33 (73.3%)	
Tumor status[a] [n (%)]				
T1	105 (70.5%)	75 (72.1%)	30 (66.7%)	0.636
T2	44 (29.5%)	29 (27.9)	15 (33.3%)	
Grading[a] [n (%)]				
G1	29 (20.4%)	22 (22.4%)	7 (15.95)	0.012
G1–2	1 (0.7%)	1 (1.0%)	0 (0.0%)	
G2	87 (61.3%)	63 (64.3%)	24 (54.5%)	
G2–3	4 (2.8%)	4 (4.1%)	0 (0.0%)	
G3	21 (14.8%)	8 (8.2%)	13 (29.9%)	
Recurrence-free survival[a] [mean (95%CI) in months]	76.1 (70.7–81.6)	75.9 (69.7–82.2)	72.3 (62.7–81.8)	

[a] Based on available cases.

Table 3
Neck dissection recurrence.

	N−	N+
Recurrence contralateral	3	0
Recurrence ipsilateral	7	4

N, nodal status.

4. Discussion

With high rates of 20%–40% for occult metastasis in the neck in OSCC patients in general, ipsilateral elective neck dissection (END) is recommended, instead of only careful clinical observation in all diagnosed patients (Fasunla et al., 2011; Wolff et al., 2012). Although this strategic approach is more accepted for OSCCs in general, some uncertainty remains with regard to carcinomas of the tongue. In more extensive tumors that have begun to cross the tongue's midline, a more severe surgical therapy may be advocated, but for early-stage OTSCCs, this issue continues to be debatable (Koo et al., 2006; Lim and Choi, 2007; Lim et al., 2006).

The authors' aim here has been to facilitate decisions regarding the optimal extent of END in early unilateral OTSCCs and, ultimately, to contribute to the further goal of developing specific treatment guidelines. After a review of the retrospective study data from both departments, positive lymph nodes were found in 35 of 150 patients (23.3%). Overall, 18 patients (12%) had nodal metastasis during the further course of their disease and, following a deeper look at the type of END performed, we found that 14 patients (13.3%) were in the solely ipsilateral END group (group A) and 4 patients (8.9%) in the END on both sides group (group B). For group A, 11 patients (78.6%) had their later nodal metastasis on the ipsilateral side, i.e., where the previous END had been performed. In 3 cases (21.4%), however, the nodal metastasis was on the contralateral side. Thus, these specific patients might have profited from a more extensive END (2.9%; 3/105 patients). With regard to the END that had been performed on both sides of the neck (group B), lymph node metastasis was found in 12 patients (26.7%) directly postoperatively. All of these positive nodes were on the ipsilateral neck side, with none on the contralateral side. Patients with such a contralateral metastasis will be the ones showing possible benefits from the two-sided END surgery method. Of the 4 patients (8.9%) with later nodal metastasis in the bilateral END group, 3 exhibited metastasis on the ipsilateral neck (75%) and 1 on the contralateral side (25%). Both END methods showed similar results in the evaluated parameters (Table 1), and no statistical differences could be observed concerning metastasis-free survival (Table 2, Fig. 2).

The key question that arises from these data, namely, whether these differences justify more extensive surgical treatment for all affected OTSCC patients, is difficult to answer, and this issue definitely needs to be clarified with more extensive research. However, based on the available data, we can in general recommend bilateral END to be performed in strictly unilateral T1/T2 tongue carcinomas. The present study data have shown values for occult metastasis of 23.3% concerning the overall population. Given these high rates in a patient group that preoperatively exhibited only slight clinical tumor progression, a more extensive treatment approach at an early stage could thus be justified. As shown by the results, the contralateral spread of lymph node metastasis is possible even at early stages of strictly unilateral carcinomas. Therefore, if the patient is in good general health and is not at high risk for predictable sequelae from the extensive surgical treatment, a sensible solution might be to dissect both neck sides directly. Although the differences between the uni- and bilateral procedures are only minor, the possible oncologic benefit from the bilateral treatment could nevertheless justify this decision in the end. On the other hand, these differences, which are not highly incisive, might facilitate the decision to spare the second neck side in medically constrained cases, as their lack of such treatment might not be too disadvantageous.

In the reported literature, other studies, such as that by Lim et al. (Lim and Choi, 2007; Lim et al., 2006), show a similar rate of bilateral metastasis in unilateral cT2N0 primaries of 4%, and advocate careful clinical observation of the contralateral neck. The study by Keski-Santti et al. (2006) also arrived at rates of 3% for bilateral lymph node metastasis, whereas other studies, e.g., by De Zinis et al. (2006), have determined bilateral lymph node metastasis exclusively in midline tumor primaries. As a common observation, Kowalski et al. (1999) have reported a much higher risk of up to 50% for contralateral lymphatic metastasis, if the primary is located on the floor of the mouth in contrast to tongue primaries, although these observations have not proved to be statistically significant. Concerning the estimation of the individual metastatic risk profile for OSCC patients in general, various studies have focused on the identification of clinical or pathological influence parameters. For maxillary OSCC, cervical metastasis rates of 29.3% can be observed, with 13% being delayed metastasis with a manifestation after an average period of 11.17 months. In this study, the anatomical location and histological grade significantly influence metastatic neck disease (see also Troeltzsch et al., 2016).

Another common question is whether clinical and pathologic parameters vary in different OSCC age groups. A study addressing this hypothesis by Troeltzsch et al. (2014) has shown that the most common site for OSCC in young patients was the oral tongue at 63%, with only one patient having been exposed to the classic risk factors. Human papillomavirus (HPV) was distributed equally among the different age groups in this study, leading to the conclusion that HPV was not an age-related independent risk factor for OSCC, whereas the anatomic predilection site and the association with classic risk factors were.

Throughout the literature in general, the mentioned overall high rates of occult metastasis for OSCC has led to the recommendation by most authors of at least an ipsilateral END for cN0 OTSCC patients, as an increase in patient survival rates can be observed (Franceschi et al., 1993; Haddadin et al., 1999).

An alternative solution, which has recently been evaluated, is the sentinel lymph node biopsy (SLNB). Performed studies have suggested that SLNB is applicable for the management of cN0 patients with early-stage OTSCC (Sagheb et al., 2014) and indicate that both neck sides can be staged (Pezier et al., 2012) with the advantages of observed better quality of life and a reduction in postsurgical complications (Murer et al., 2011; Schiefke et al., 2009). The higher false-negative rates and lower sensitivity are significant disadvantages when compared with classic END, and so further research with larger study populations is needed to clarify whether SNLB is an equally safe alternative.

One possible attempt to find an adequate middle-course solution may be to look more precisely at the advantages and disadvantages of END for each specific patient case. On the one hand, a bilateral surgical neck procedure comes with longer operation durations, greater wound areas, and more operative stress to the patient, and thus could ultimately lead to an increase in patient morbidity and surgical complications. On the other hand, it could result in a higher chance of cure and possibly help to prevent later lymph node metastasis. Furthermore, the more extensive bilateral gathering of lymph nodes from both neck sides for postoperative histopathological examination could lead to more information for making the necessary decisions regarding suitable adjuvant therapy. Advocates of bilateral END also point out that if both neck sides are treated, this often leads to an aesthetically superior outcome, because of the symmetry of equal access scars on both neck sides.

5. Conclusion

We can conclude that, if the patient shows no signs advising against a more extended surgical neck dissection treatment, END should be performed directly on both neck sides. The advantages of the more detailed histopathological findings, the aesthetically more appealing neck outcome, and the higher oncologic safety make this a sensible option, although one should not forget the individuality of the specific patient case. The general health status, comorbidities, and individual tumor risk profile always need to be considered when deciding on the extension END that seems the most suitable. In cases of doubt, the decision regarding treatment strategy should be made by a tumor board with the involvement of all necessary medical disciplines. As the treatment of oral cancer nowadays has become an interdisciplinary task, it should be limited to experienced cancer treatment centers only. The two evaluated END procedures in this study show similar results in the examined parameters, and thus both methods remain well-established tools for the experienced head and neck surgeon, given the right indication.

Conflicts of interest

None declared.

References

Aggarwal S, Devaraja K, Sharma SC, Das SN: Expression of vascular endothelial growth factor (VEGF) in patients with oral squamous cell carcinoma and its clinical significance. Clin Chim Acta 436: 35–40, 2014

De Zinis LO, Bolzoni A, Piazza C, Nicolai P: Prevalence and localization of nodal metastases in squamous cell carcinoma of the oral cavity: role and extension of neck dissection. Eur Arch Oto-Rhino-Laryngol 263: 1131–1135, 2006

Dogan E, Cetinayak HO, Sarioglu S, Erdag TK, Ikiz AO: Patterns of cervical lymph node metastases in oral tongue squamous cell carcinoma: implications for elective and therapeutic neck dissection. J Laryngol Otol 128: 268–273, 2014

Fasunla AJ, Greene BH, Timmesfeld N, Wiegand S, Werner JA, Sesterhenn AM: A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol 47: 320–324, 2011

Franceschi D, Gupta R, Spiro RH, Shah JP: Improved survival in the treatment of squamous carcinoma of the oral tongue. Am J Surg 166: 360–365, 1993

Grandi C, Alloisio M, Moglia D, Podrecca S, Sala L, Salvatori P, et al: Prognostic significance of lymphatic spread in head and neck carcinomas: therapeutic implications. Head Neck Surg 8: 67–73, 1985

Haddadin KJ, Soutar DS, Oliver RJ, Webster MH, Robertson AG, MacDonald DG: Improved survival for patients with clinically T1/T2, N0 tongue tumors undergoing a prophylactic neck dissection. Head Neck 21: 517–525, 1999

Huang SF, Kang CJ, Lin CY, Fan KH, Yen TC, Wang HM, et al: Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. Cancer 112: 1066–1075, 2008

Keski-Santti H, Atula T, Tornwall J, Koivunen P, Makitie A: Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. Oral Oncol 42: 96–101, 2006

Khafif A, Lopez-Garza JR, Medina JE: Is dissection of level IV necessary in patients with T1-T3 N0 tongue cancer? Laryngoscope 111: 1088–1090, 2001

Koo BS, Lim YC, Lee JS, Choi EC: Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head Neck 28: 896–901, 2006

Kowalski LP, Bagietto R, Lara JR, Santos RL, Tagawa EK, Santos IR: Factors influencing contralateral lymph node metastasis from oral carcinoma. Head Neck 21: 104–110, 1999

Kyzas PA, Stefanou D, Batistatou A, Agnantis NJ: Potential autocrine function of vascular endothelial growth factor in head and neck cancer via vascular endothelial growth factor receptor-2. Mod Pathol 18: 485–494, 2005

Lim YC, Choi EC: Unilateral, clinically T2N0, squamous cell carcinoma of the tongue: surgical outcome analysis. Int J Oral Maxillofac Surg 36: 610–614, 2007

Lim YC, Lee JS, Koo BS, Kim SH, Kim YH, Choi EC: Treatment of contralateral N0 neck in early squamous cell carcinoma of the oral tongue: elective neck dissection versus observation. Laryngoscope 116: 461–465, 2006

Moore SR, Johnson NW, Pierce AM, Wilson DF: The epidemiology of tongue cancer: a review of global incidence. Oral Dis 6: 75–84, 2000

Murer K, Huber GF, Haile SR, Stoeckli SJ: Comparison of morbidity between sentinel node biopsy and elective neck dissection for treatment of the n0 neck in patients with oral squamous cell carcinoma. Head Neck 33: 1260–1264, 2011

Pezier T, Nixon IJ, Gurney B, Schilling C, Hussain K, Lyons AJ, et al: Sentinel lymph node biopsy for T1/T2 oral cavity squamous cell carcinoma—a prospective case series. Ann Surg Oncol 19: 3528–3533, 2012

Pianka A, Knosel T, Probst FA, Troeltzsch M, Woodlock T, Otto S, et al: Vascular endothelial growth factor receptor isoforms: are they present in oral squamous cell carcinoma? J Oral Maxillofac Surg 73: 897–904, 2015

Prince S, Bailey BM: Squamous carcinoma of the tongue: review. Br J Oral Maxillofac Surg 37: 164–174, 1999

R-Core-Team: R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: http://www.r-project.org/; 2015

Robbins KT, Clayman G, Levine PA, Medina J, Sessions R, Shaha A, et al: Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg 128: 751–758, 2002

Robert Koch Institut: Krebs in Deutschland 2011/2012. Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Berlin 10; 2015, 26–29

Sagheb K, Sagheb K, Taylor KJ, Al-Nawas B, Walter C: Cervical metastases of squamous cell carcinoma of the maxilla: a retrospective study of 25 years. Clin Oral Invest 18: 1221–1227, 2014

Sano D, Myers JN: Metastasis of squamous cell carcinoma of the oral tongue. Cancer Metastasis Rev 26: 645–662, 2007

Schiefke F, Akdemir M, Weber A, Akdemir D, Singer S, Frerich B: Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck 31: 503–512, 2009

Schuller DE, McGuirt WF, McCabe BF, Young D: The prognostic significance of metastatic cervical lymph nodes. Laryngoscope 90: 557–570, 1980

Shah JP, Candela FC, Poddar AK: The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer 66: 109–113, 1990

Silver CE, Moisa II: Elective treatment of the neck in cancer of the oral tongue. Semin Surg Oncol 7: 14–19, 1991

Talamini R, Bosetti C, La Vecchia C, Dal Maso L, Levi F, Bidoli E, et al: Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control 13: 957–964, 2002

Therneau T, Gambusch P: A package for survival analysis in S. Available at: http://cran.r-project.org/web/packages/survival; 2015

Troeltzsch M, Knosel T, Eichinger C, Probst F, Troeltzsch M, Woodlock T, et al: Clinicopathologic features of oral squamous cell carcinoma: do they vary in different age groups? J Oral Maxillofac Surg 72: 1291–1300, 2014

Troeltzsch M, Knosel T, Woodlock T, Troeltzsch M, Pianka A, Probst FA, et al: Are there clinical or pathological parameters of maxillary oral squamous cell carcinoma with an influence on the occurrence of neck node metastasis? An appraisal of 92 patients. J Oral Maxillofac 74: 79–86, 2016

Wolff KD, Follmann M, Nast A: The diagnosis and treatment of oral cavity cancer. Deutsches Arzteblatt Int 109: 829–835, 2012

Yuen AP, Wei WI, Wong YM, Tang KC: Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. Head Neck 19: 583–588, 1997

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Publications

Head and Neck Salivary Gland Carcinomas—Elective Neck Dissection, Yes or No?.
NOBIS CP, ROHLEDER NH, WOLFF KD, WAGENPFEIL S, SCHERER EQ, KESTING MR.
Journal of Oral and Maxillofacial Surgery, 2014.

Development of a haptic model for teaching in reconstructive surgery – the radial forearm flap.
NOBIS CP, BAUER F, ROHLEDER NH, WOLFF KD, KESTING MR.
Simulation in Healthcare, 2013.

Elective neck dissection in unilateral carcinomas of the tongue - unilateral vs. bilateral approach.
NOBIS CP, OTTO S, GRIGORIEVA T, ALNAQBI M, TROELTZSCH M, SCHÖPE J, WAGENPFEIL S, EHRENFELD M, WOLFF KD, KESTING MR.
Journal of Cranio-Maxillofacial Surgery, 2017

Amniotic membrane in oral and maxillofacial surgery.
KESTING MR, WOLFF KD, **NOBIS CP**, AND ROHLEDER NH.
Oral Maxillofac Surg, 2012.

[Sandwichtechnik bei ausgedehnten Mund-, Kiefer-, Gesichtsdefekten – Rekonstruktionen mit gedoppelten, mikrovaskulär-gestielten Transplantaten].
KESTING MR, **NOBIS CP.**
Face – international magazine of orofacial esthetics; 7. Jahrgang, September, 3/2013; ISSN 1864-4279

Design of a Haptic Model for the Training of Cleft Treatment Procedures.
RAU A, **NOBIS CP**, BEHR AV, KESTING MR.
Simulation in Healthcare, 2015

Surface-optimized free flaps for complex facial defects after skin cancer.
KESTING MR, MACIVER C, WALES CJ, WOLFF KD, **NOBIS CP**, ROHLEDER NH.
Journal of Craniomaxillofacial Surgery, 2015

Sandwich flaps as a feasible solution for the management of huge mandibular composite tissue defects.
WEITZ J, KREUTZER K, BAUER FJ, WOLFF KD, **NOBIS CP**, KESTING MR.
Journal of Craniomaxillofacial Surgery, 2015

An expression analysis of markers of radiation-induced skin fibrosis and angiogenesis in wound healing disorders of the head and neck.
KOERDT S, ROHLEDER NH, ROMMEL N, **NOBIS CP**, STOECKELHUBER M, PIGORSCH S, DUMA MN, WOLFF KD, KESTING MR.
Radiation Oncology, 2015

Classification of orbital exenteration and reconstruction.
KESTING MR, KOERDT S, ROMMEL N, MÜCKE T, WOLFF K-D, **NOBIS CP**, RINGEL F, FROHWITTER G.
Journal of Cranio-Maxillofacial Surgery, 2017

Vorträge

Adhesiolysis after fractures of the orbital floor by membranes laminated with amniotic membrane;
NOBIS CP, ROHLEDER NH, STEINSTRAESSER L, KOLK A, KESTING MR.
4th European Plastic Surgery Research Council (EPSRC) 2012, 23.-26.08.2012, Hamburg, Deutschland.

Ist eine HPV-Infektion bei non-smoker-, non-drinker-Patienten im weiblichen Senium der Risikofaktor für die Entstehung von Mundhöhlenkarzinomen?
NOBIS CP, ROHLEDER NH, WOLFF KD, BAUER F, KESTING MR.
63. Jahrestagung der Arbeitsgemeinschaft für Kieferchirurgie (AG Kiefer) und 34. Jahrestagung des Arbeitskreises für Oralpathologie und Oralmedizin (AKOPOM); D32, AKOPOM 2, Abstract in DZZ; 09.-10.05.2013, Bad Homburg, Deutschland.

Mitgliedschaften

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