Diplomarbeit

Quality management of the interdisciplinary tumor board for head and neck cancer. Causes of the difference between primarily suggested therapy and received therapy

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Marchtrenk, 19. November 2018 *Julia Viktoria Scheuchenegger eh*

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Zusammenfassung

Einleitung:

Seit 2001 wird an der Hals-Nasen-Ohren-Universitätsklinik wöchentlich ein interdisziplinäres Tumorboard abgehalten. Expertinnen und Experten aus verschiedenen Fachgebieten diskutieren die bestmöglichen Therapieoptionen für Patientinnen und Patienten mit malignen Tumoren im Kopf-Hals-Bereich. Seit 2016 ist das Subzentrum Kopf-Hals-Tumore offiziell Teil des Comprehensive Cancer Centers der Medizinischen Universität Gaz.

Material und Methoden:

Diese Studie wurde retrospektiv durchgeführt. Die Daten wurden aus dem Krankenhausinformationssystem MEDOCS, das im Landeskrankenhaus Graz verwendet wird, gesammelt. Der Fokus lag auf Patientinnen und Patienten, die dem Tumorboard zwischen Januar 2014 und Dezember 2016 vorgestellt wurden. Das Hauptziel der Studie war es, zu überprüfen wie viele der Patientinnen und Patienten tatsächlich auch die primär durch das Tumorboard vorgeschlagene Therapie erhalten haben und welche Gründe es gab, wenn dies nicht der Fall war.

Ergebnisse:

Zwischen Januar 2014 und Dezember 2016 wurden 707 Patientinnen und Patienten im Tumorboard diskutiert. Da nur die Erstvorstellungen für diese Studie relevant waren, konnten 556 von 707 inkludiert werden. 93% der Patientinnen und Patienten erhielten die primär vorgeschlagene Therapie und 75% davon erhielten die Therapie vollständig. Die verbleibenden 25% hatten entweder eine Änderung im Therapieplan oder konnten die Behandlung nicht vollständig erhalten. Die Gründe dafür waren beispielsweise reduzierter Allgemeinzustand, Intoleranz oder Tod. In 7% der Fälle war keine ausreichende Dokumentation vorhanden, weil die Patientinnen und Patienten die Therapie verweigerten oder extern therapiert wurden.

Diskussion:

Multidisziplinäre Tumorboards sind mittlerweile unerlässlich, um Therapieentscheidungen für Patientinnen und Patienten mit Kopf-Hals-Tumoren zu treffen. Unsere retrospektive Datenanalyse zeigte zufriedenstellende Resultate. 93% aller inkludierten Patientinnen und Patienten erhielten die primär vorgeschlagene Therapie und 73,9% erhielten im weiteren Verlauf die vollständige Behandlung ohne Änderung des Therapieplans. Die Bestrahlung zeigte sich als die tolerabelste Therapieoption, da nur 11% der Strahlentherapien frühzeitig abgebrochen wurden, im Gegensatz zu 36% der Chemotherapien und 28,6% der Immuntherapien. Frauen brachen die Bestrahlung signifikant häufiger ab. Die Gründe dafür sollten in weiterführenden Studien untersucht werden. Im Bereich der Nachsorge ist die Hals-Nasen-Ohren-Universitätsklinik des LKH-Univ. Klinikum Graz dem weltweiten Standard mit 10 Jahren Follow Up Zeit und jährlicher Bildgebung voraus.

Abstract

Introduction:

Since 2001 tumor boards have taken place at weekly intervals at the department of Otorhinolaryngology-Head and Neck Surgery Graz. A panel of experts discuss the best currently available therapy options for patients with malignant tumors in the head and neck region. Since 2016 the subcenter “Head and Neck Tumors” officially is part of the Comprehensive Cancer Centre Graz.

Methods:

The study was conducted retrospectively. Patient data was collected through the hospital information system, called MEDOCS, used at the LKH-Univ. Klinikum Graz. We focused on patients introduced to the tumor board from January 2014 to December 2016. The main goal of the study was to ascertain how many of the patients received the primarily suggested treatment by the tumor board and what the reasons were within the group of patients who didn’t.

Results:

From January 2014 to December 2016 707 patients have been discussed in the tumor board. In this study we were interested only in the patients introduced to the tumor board for the first time, which were 556 out of the 707. 93% of the patients received the suggested therapy and 75% of them completed the therapy. The other 25% underwent a change in their therapy plan or they couldn’t undergo the full treatment due to reasons like reduced general condition, intolerances or death. For 7% there was no documentation of the treatment undertaken because either the patient refused the therapy, or the patient was treated in another hospital.

Discussion:

Multidisciplinary tumor boards have become indispensable when making therapy decisions for head and neck cancer patients. Our retrospective data analyses of the tumor board patient data showed satisfactory results. 93% of all included patients received the primarily suggested therapy and 73.9% completed therapy according to the treatment plan without any changes. Radiation therapy seems to be the most tolerable therapy option as only 11% of radiotherapies were terminated early, in comparison to 36% of all chemotherapies and 28.6% of all immunotherapies.

Women were significantly more likely to terminate radiation than men. The reasons for this should be further investigated. In terms of follow up care the clinic for otorhinolaryngology of the LKH-Univ. Klinikum Graz is ahead of common standards worldwide with 10 years of follow up care with yearly imaging.

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List of Abbreviations

AJCC	American Joint Committee on Cancer
CUP	carcinoma of unknown primary
CT	Computer Tomography
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr-virus
ECOG	Eastern Cooperative Oncology Group
HIV	human immunodeficiency virus
HPV	human papilloma virus
IARC	International Agency for Research on Cancer
LKH	Landeskrankenhaus
MRI	Magnetic Resonance Imaging
ND	Neck dissection
PET	Positron Emission Tomography
SCC	squamous cell carcinoma
TCF	Docetaxel, Cisplatin, 5-Fluoruracil
UICC	International Union against Cancer
WHO	World Health Organization

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1 Introduction

For 15 years the head and neck tumor board has taken place weekly at the department of Otorhinolaryngology-Head and Neck Surgery Graz. Experts from different medical facilities such as oncology, pathology, radiology, radiation medicine or otorhinolaryngology discuss patients suffering from cancer in the head and neck region and work out an individual therapy concept for each patient. Since 2016 the subcenter “Head and Neck Tumors” officially is part of the Comprehensive Cancer Centre Graz.

1.1 Goal

The first aim of this study was to ascertain how many of the patients received the treatment suggested by the tumor board. The second aim was to determine how many of those received the full treatment without any changes of the therapy plan or termination of the therapy. Additionally, we tried to objectify the reasons for not receiving the therapy at the beginning or during ongoing therapy. The intent is to ensure and maintain a high standard of quality when it comes to decisions regarding and execution of therapy plans.

1.2 Global Epidemiology

Cancer in the head and neck area is a great problem around the globe and numbers are rising. Head and neck cancers are the ninth most common malignancies in the world (Gupta, Johnson et al. 2016). Especially malignancies of the oral cavity and the oropharynx are very common in most parts of the world.

According to the International Agency for Research on Cancer (IARC) incidence rates vary greatly all over the world. Countries with high incident rates can be found in Europe, South America or South and Southeast Asia. The global age-standardized incidence ratio in 2012 was led by Papua New Guinea with 29.3 cases per 100 000. Second and third were Hungary (23.8 per 100 000) and Bangladesh (21.4 per 100 000), respectively.

The same countries have to be named when speaking of mortality rates. Again, Papua New Guinea is in the lead with 19.2 deaths per 100 000, followed by Bangladesh and Hungary with 15.2 and 12.3 deaths per 100 000, respectively.

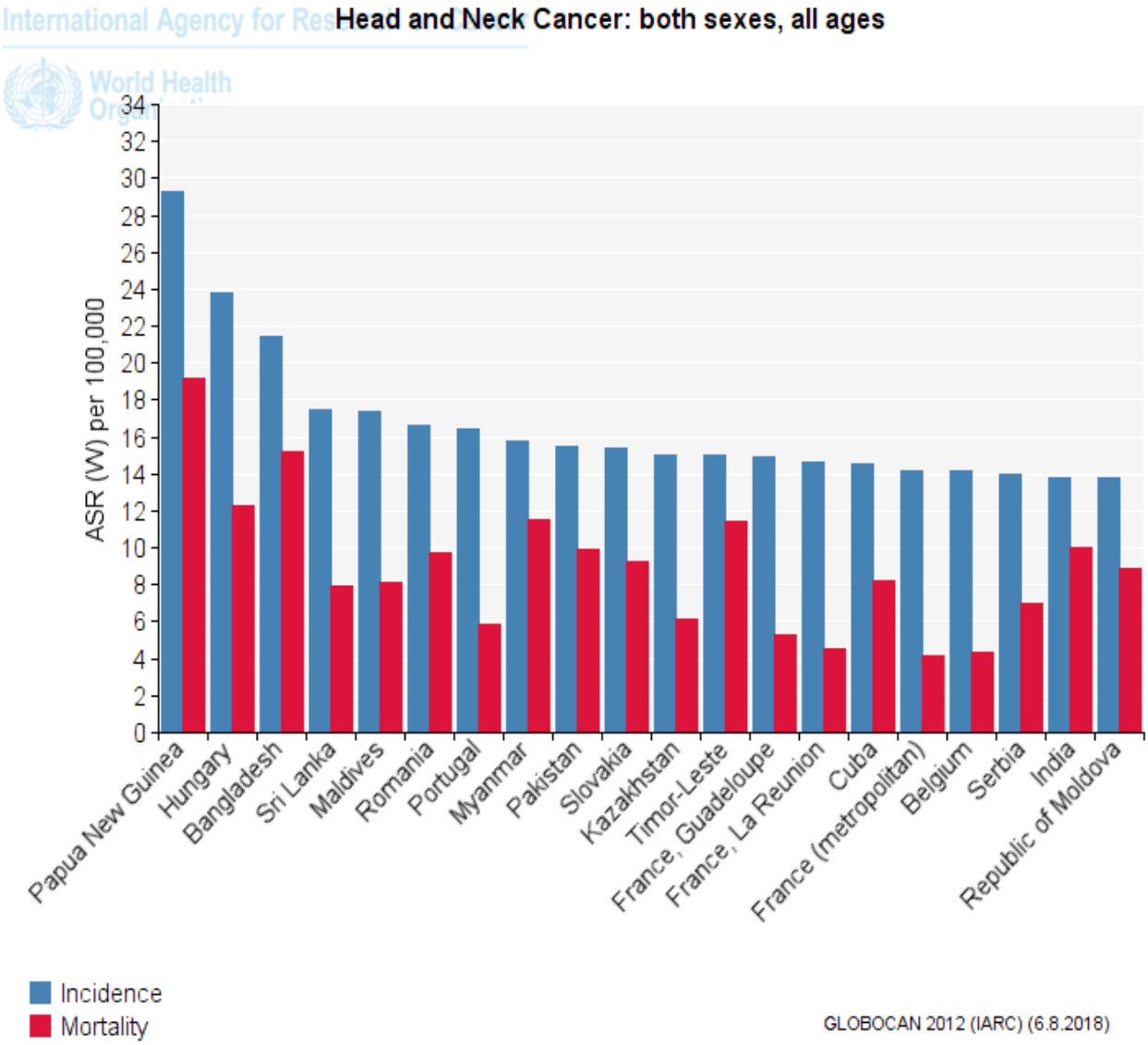

Figure 1) Ranking of age-standardized incidence and mortality rates or lip, oral cavity, oropharyngeal and laryngeal cancer worldwide according to IARC (2012) (Ferlay, Soerjomataram et al.)

Age-standardized incidence ratio in Austria is 9.8 cases per 100 000 and age-standardized mortality ratio 3.4 deaths per 100 000 (Ferlay, Soerjomataram et al.).

2.4 TNM-Staging System

The TNM system, developed by Pierre Denoix between 1943 and 1952, has brought considerable benefits by standardizing the description and reporting of cancers worldwide. The system helps prognosticate by categorizing malignant tumors (Paleri, Mehanna et al. 2010).

There have been several updates of the TNM-staging system, the most recent (8^{th}) edition was published in December 2016 and came into effect on January 1, 2017. The TNM-staging system used (and described) for this study, however, is the 7^{th} edition, because the collected data originates from before 2017, when patients were staged according to the 7^{th} edition of the TNM system.

1.3 Entities of Head and Neck Cancers

Usually malignancies of the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, paranasal sinuses and salivary glands are included in head and neck cancers (Bose, Brockton et al. 2013). In this study we also included several other types of malignant tumors. This is mainly due to the various diagnoses that were found in the tumor board patients. 17 groups were defined, including malignancies of the larynx, hypopharynx, oropharynx, oral cavity/base of the mouth, epipharynx, paranasal sinuses, lymph nodes, parotis, carcinomas of unknown primary (CUP), squamous cell carcinomas of the skin, malignancies of the lacrimal duct, the submandibular glands, soft tissue tumors, carcinomas of the nose and others as the last group.

1.3.1 Larynx/Hypopharynx

Tumors of the larynx and hypopharynx are usually described together due to their anatomic and functional closeness. Malignant tumors in this region occur six times more often in men than women. The numbers, however, are rising in both sexes, which is a result of the etiological main factor: chronic smoking. Apart from cigarette smoking, exposition to other carcinogens, such as asbestos, chromate, benzene or nickel can cause malignancies of the larynx-/hypopharynx as well (Thurnher, Grasl et al. 2011, Boenninghaus, Lenarz 2007).

The most common type of carcinomas in the larynx/hypopharynx are carcinomas of the glottis. Histologically 95% of which are SCCs, the rest are adeno- or undifferentiated carcinomas. The advantage of glottis malignancies is that symptoms, such as hoarseness often occur at a very early stage, which leads to early detection and a good prognosis as small tumours of the glottis can often be easily (laser-)resected (Böcker, Denk et al. 2008, Boenninghaus, Lenarz 2007).

Other symptoms than hoarseness can be globus sensation, difficulty breathing, pain in the throat or radiating to the ears and haemoptysis (Thurnher, Grasl et al. 2011).

	HYPOPHARYNX
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to 1 subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than 1 subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Table 1) Staging system of hypopharyngeal cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Lanzer 2012, Paleri, Mehanna et al. 2010)

For classification of the larynx, the region is divided into supraglottis, glottis and subglottis:

	LARYNX
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
	SUPRAGLOTTIS
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of the base the of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Tumor invades through the thyroid cartilage and /or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
	GLOTTIS
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep

	extrinsic muscles of the tongue, strap muscles, thyroid or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery or invades mediastinal structures
	SUBGLOTTIS
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or involves mediastinal structures

Table 2) Staging system of laryngeal cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Lanzer 2012, Paleri, Mehanna et al. 2010)

1.3.2 Oropharynx

Three different types of tumors occur in the area of the oropharynx, often originating from the tonsils or surrounding lymphatic tissue: carcinomas (and transitional cell carcinomas), lymphoepithelial tumors and malignant lymphomas. The largest fraction by far are the carcinomas. Tumor growth in the oropharynx often results in early symptoms. These symptoms include difficulties swallowing (especially one-sided), otalgia, muffled speech and lockjaw (Boenninghaus, Lenarz 2007).

The oropharyngeal squamous cell carcinoma has increased in the last years, similar to SCCs of the larynx/hypopharynx. Osazuwa-Peters, Simpson et al. for example have shown that there was an overall increase in incidence of 57,3% between 1975 and 2014 in the United States (Osazuwa-Peters, Simpson et al. 2017).

Tumor stadium is usually determined after panendoscopic examination according to TNM-Staging-System:

	OROPHARYNX
TX	Primary Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
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 or extension to lingual surface of epiglottis
T4a	Tumor invades the larynx, deep muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx or skull base or encases carotid artery

Table 3) Staging system of oropharyngeal cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Paleri, Mehanna et al. 2010, Lanzer 2012, Thurnher, Grasl et al. 2011)

1.3.3 Oral cavity

Oral SCCs account for 3-4% of all malignant tumors in Europe and the United States. Most commonly they occur in the sixth and seventh decade of life (Böcker, Denk et al. 2008).

Malignancies of the oral cavity often are associated with alcohol- and nicotine abuse, and bad hygiene. Less commonly they can occur after mechanical irritation which can be caused by (ill-fitting) prostheses or teeth or as a consequence of the Plummer-Vinson-Syndrome and Mb. Bowen. The malignant tumor often develops on the ground of leukoplakia. The symptoms depend on the localization and can comprise burning pain, foetor ex ore, salivation, difficulties swallowing and limited tongue mobility. Histologically malignancies in this area are almost always squamous cell carcinomas. A rarer kind of malignancy in this area is the Kaposi-Sarcoma, which usually occurs in immunocompromised patients (e.g. HIV). In 20 – 25% the Kaposi-Sarcoma first manifests in the oral cavity (gingiva, tongue and hard palate) (Boenninghaus, Lenarz 2007).

Classification is similar to the classification of oropharyngeal cancers:

	ORAL CAVITY
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
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	Tumor invades through cortical bone, into deep muscle of tongue, maxillary sinus, or skin of face
T4b	Tumor involves masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Table 4) Staging system of oral cavity cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Paleri, Mehanna et al. 2010, Lanzer 2012)

1.3.4 Nasopharynx

Tumors with the primum in the Epi- or Nasopharynx occur quite rarely, which makes it difficult for one hospital to accumulate a sufficient number of cases. Again, malignancies in this area usually are SCCs, but there also may occur lymphoepithelial tumors, undifferentiated tumors and lymphomas. Ventilation disorder of the tuba auditiva often is the first symptom. Subsequently, impeded nasal breathing and mucous, as well as purulent or bloody secretion is possible. With larger expansion of the tumor even cranial nerves might be constricted resulting in paralysis of the ocular muscles or trigeminal neuralgia.

Complete surgical resection is almost never possible due to the complexity of the region, the closeness to the cranial base and the usually late detection. Overall survival of 5 years is only about 15% although it may range up to 50% if the tumor is sensitive to radiation (Boenninghaus, Lenarz 2007).

For tumors of the epipharynx TNM classification is determined according to the number of affected structures:

	NASOPHARYNX
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to nasopharynx, or extends to oropharynx and/or nasal cavity
T2	Tumor with parapharyngeal extension
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space

Table 5) Staging system of nasopharyngeal cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Lanzer 2012, Paleri, Mehanna et al. 2010)

1.3.5 Nasal cavity and Paranasal Sinuses

Similar to the nasopharyngeal carcinomas, malignancies of the nasal cavity and paranasal sinuses are quite rare. The different histological types and subsites, with proximity of sensitive organs, add to the complexity this disease. The following histological types can be found: mostly SCCs with 55%, second to that adenocarcinomas with 29% (Thorup, Sebbesen et al. 2010), adenoid-cystic carcinomas and rare forms like myoepithelial carcinomas, undifferentiated carcinomas or esthesioneuroblastomas. Thorup et al. showed that tumors in this area are often presented at a late stage. Out of 242 patients 26% were diagnosed at stage 3 and 47% at stage 4. The most common localization is the maxillary sinus. Adenocarcinomas usually are connected to chronic exposure to hardwood-dust (e.g. oak, beech) and recognized as occupational disease. A high-risk group are therefore carpenters or parquet layers (Böcker, Denk et al. 2008).

Symptoms of malignancies of the nasal cavity and the paranasal sinuses depend on the localization and often occur only at a very late stage. Tumors of the upper level (maxillary sinus roof, ethmoid bone and frontal sinus) can cause double images if they invade the eye socket. Tumors of the middle level (maxillary sinus and lateral nose wall) can impede nasal breathing, cause secretion of bloody, purulent, smelling mucous, and severe pain if the dura is affected. Tumors of the lower level (alveolar

process, palate, basis of the maxillary sinus) can protrude into the palate or the alveolar process. Thus, toothache or tooth loosening can occur (Boenninghaus, Lenarz 2007).

The TNM classification of maxillary carcinomas differs from the classification of carcinomas of the nasal cavity and ethmoidal cells:

	MAXILLARY CARCINOMAS
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to maxillary mucosa, without bone arrosion
T2	Tumor erodes or destroys bone, invades the hard palate and/or the middle nasal meatus without extension to the posterior wall of the maxillary sinus, subcutaneous soft tissue, medial wall/flor of the orbit, ethmoidal sinus or the pterygoid fossa
T3	Tumor erodes or destroys the posterior wall of the maxillary sinus, subcutaneous soft tissue, medial wall/floor of the orbit, ethmoidal sinus or pterygoid fossa
T4a	Tumor invades contents of the anterior orbit, skin of the cheek, pterygoid process, infratemporal fossa, cribriform plates, sphenoidal sinus or frontal sinus
T4b	Tumor invades the apex of the orbit, dura, brain, middle cranial fossa, cranial nerves, nasopharynx or the clivus of Blumenbach

Table 6) Staging system of maxillary cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Paleri, Mehanna et al. 2010)

Tumors of the nasal cavity and ethmoidal cells are categorized by affected anatomic sites and subsites:

NASAL CAVITY AND ETHMOIDAL CELLS	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of the nasal cavity or the ethmoidal sinus with or without bone invasion
T2	Tumor extends to two subsites in one region or extends to on adjacent region in the nasoethmoidal complex, with or without bone arrosion
T3	Tumor invading medial wall or floor of the orbit, or maxillary sinus, hard palate or lamina cribrosa
T4a	Tumor invading one or more of the following: content of the orbit, skin of the nose or the cheek, minimal extension to the anterior cranial fossa, the pterygoid process, the sphenoidal or the frontal sinus
T4b	Tumor invades the apex of the orbit, dura, brain, middle cranial fossa, cranial nerves, nasopharynx or the clivus of Blumenbach

Table 7) Staging system of nasal cavity and ethmoidal cell cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Paleri, Mehanna et al. 2010)

1.3.6 Parotid and Submandibular Glands

Tumors of the salivary glands account for 3% of head and neck tumors and are located in the parotid gland in about 80%. The classification was updated by WHO in 2005 and recognizes now 24 types of malignant epithelial neoplasms that may be observed within the parotid gland. Moreover, there are a variety of non-epithelial tumor-like growths, lymphoproliferative disorders and secondary malignancies like metastases to be found in the parotid gland. This histopathological variety is quite unique and can make diagnosing a challenge. The most commonly found malignant tumors in the parotid gland are acinic cell carcinomas (23%) and adenocarcinomas (13%) (Dzaman, Pietniczka-Zaleska et al. 2016, Coombe, Lam et al. 2016).

Symptoms caused by tumors in the parotid gland can be a palpable often painless nodular hardening, ulceration to the skin or to the auditory canal, pain if the tumors protrudes into the retromandibular fossa and facial nerve palsy.

Due to the many histological subtypes it is difficult to determine an exact 5-year survival rate. It ranges between 20 and 50%.

	PAROTID GLAND
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension, without extension to extra-parenchymal tissue
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension, without extension extra-parenchymal tissue
T3	Tumor more than 4 cm in greatest dimension and/or with extension to extra-parenchymal tissue
T4a	Tumor invades skin, mandible, external auditory canal or the facial nerve
T4b	Tumor invades cranial base, pterygoid process or encases internal carotid artery

Table 8) Staging system of parotid gland cancers according to the seventh edition of the TNM-Staging System of the UICC and the AJCC (Thurnher, Grasl et al. 2011, Paleri, Mehanna et al. 2010)

1.3.7 Carcinoma of unknown primary

A Carcinoma of unknown primary (CUP) is defined as a histologically confirmed metastasis of a malign tumor in one or several lymphatic nodes on one or both sides of the neck without detected primary site. It is possible that the primary tumor is detected only ever after the therapy, post mortem or never. 5 – 10% of all malign lymph node swellings are CUPs.

The metastasis can be identified as SCCs, undifferentiated carcinomas, lymphoepithelial carcinomas, adenocarcinomas and many others. When a metastasis of the cervical lymph nodes is detected it leads to intensive search for the primary tumor (panendoscopy, sonography, bronchoscopy, gastroduodenoscopy, coloscopy, biopsy samples, PET, …). Most likely the primary tumor site is the head and neck region (70%). If no primary tumor site can be found,

the diagnosis is CUP. Therapy depends on the histological findings and on the result of the EBV-serology and can comprise surgery and/or radiation. Patients have to undergo a very careful follow up as the primary tumor may still manifest (Arnold, Ganzer 2005, Fehri, Rifi et al. 2013).

1.3.8 Squamous Cell Carcinomas

Squamous cell carcinomas (SCCs) are aggressive tumors originating from the squamous cell epithelium (skin, mucous membranes of the esophagus, upper aerodigestive tract, vagina, epithelium of the gallbladder, …) and can occur with or without cornification.

Macroscopically squamous cell carcinomas are endophytically growing, nodular and often ulcerated tumors. More scarcely exophytically growing tumor forms are possible, usually these are highly differentiated.

Histologically tumor cells appear big, polygonal or spindle-shaped and show nuclear atypia. Three degrees of differentiation are distinguished (G1 – G3): G1: highly differentiated, G2: moderately differentiated, G3: poorly differentiated; G1 showing the largest similarity to the original tissue and G3 showing little or no similarity to the original tissue (Böcker, Denk et al. 2008).

1.4 Risk Factors

There are multiple risk factors for developing a carcinoma in the head and neck area: alcohol and tobacco, fruits, certain diets and viruses like HPV and EBV (Lanzer 2012).

1.4.1 Alcohol and Tobacco

Alcohol and tobacco smoking are the strongest independent risk factors for development of a malignancy in the head and neck area and have a synergistic effect (Dal Maso, Torelli et al. 2016). Dhull, Atri et al. found that 89% of all head and neck cancer patients are smokers, and 59% alcoholics. 53% are using tobacco as

well as alcohol (Dhull, Atri et al. 2018). According to Curado et al. the total amount of alcohol consumed over a lifetime plays a more important role than the kind of alcohol consumed (Curado, Hashibe 2009).

There are countless studies throughout the literature showing that tobacco is a cancerogenic substance, especially affecting the upper aerodigestive tract. For cancers of the oral cavity, pharynx, larynx and esophagus, the risk steadily increases with increasing number of smoked cigarettes per day according to Polesel, Talamini et al. They also demonstrated that the risk of developing oral, pharyngeal, and esophageal cancers was significantly higher for smokers, beginning with as low as 2 cigarettes per day (Polesel, Talamini et al. 2008).

1.4.2 EBV

The Epstein-Barr-virus (EBV) is a B-lymphotropic Virus which infects over 90% of the population worldwide. It is spread through aerosol inhalation (airborne droplet infection) and infects B-lymphocytes where it persists lifelong. If the primary infection takes place at a young age it is usually asymptomatic. Primary infection later in life (adolescent age) can result in infectious mononucleosis, a self-limitating lymphoproliferative feverish disease. It generally passes after a few days to weeks. Nevertheless, in some cases complications, such as hepatitis, splenomegaly, rupture of the spleen or pneumonia) can occur. Very rarely the infection can take a fulminant and deadly course, usually in immunocompromised patients. The latent infection with EBV can be reactivated if the immune system of the patient is weakened. This is when the virus develops its oncogenic potential (Böcker, Denk et al. 2008).

LMP1 is thought to be the EBV oncogene as it has transforming ability in rodent fibroblasts. Expression of this protein has many different effects in the human body, including effects on epithelial cell growth and differentiation and it induces morphologic transformation of some cell lines and EFGR expression (Raab-Traub 2002).
EBV is connected to the development of several kinds of malignancies: Burkitt-lymphoma, Hodgkin-lymphomas, non-Hodgkin-lymphomas, but also

nasopharyngeal carcinomas are known to be associated with EBV. Tatli Dogan, Kilicarslan et al. found that 87% patients with nasopharyngeal carcinoma were EBV-positive. The highest rate, 95.6%, of EBV-positivity was found in undifferentiated nasopharyngeal carcinoma patients (Tatli Dogan, Kilicarslan et al. 2016).

1.4.3 HPV

The human papilloma virus belongs to the group of papilloma-, polyoma- and vacuolizing viruses (=papoaviruses). At present more than 100 types of HPV are known. Some of which are cancer-causing, also known as high-risk types (6, 11, 16, 18, 31, 33, 35, 45). They can be found in precancerous lesions, as well as in precancerous condylomata acuminata, in laryngeal papillomas, SCCs of the cervix, anus, vulva and pharynx, especially the oropharynx (Böcker, Denk et al. 2008). Papillomaviruses (PVs) are circular, double-stranded DNA viruses and are ubiquitous throughout the world. The primary oncogenic proteins expressed through papilloma viruses, E6 and E7, are thought to be largely responsible for niche adaptation, viral amplification, and inadvertently driving carcinogenesis (Mirabello, Clarke et al. 2018).

Determining the HPV status is very important as for example patients with HPV-positive oropharyngeal cancer generally respond better to chemotherapy and have a better prognosis than patients with HPV-negative cancer (Maxwell, Grandis et al. 2016).

1.5 Therapy

Although head and neck cancers remain a major problem in most countries of the world, we are in the lucky position to have access to a great variety of therapy options from surgery over chemo- and immunotherapy to radiotherapy. The therapy plan is drawn up individually for each tumor patient by the experts of the tumor board.

1.5.1 Pathway

Before it is decided which therapy is appropriate for each patient the pathway has to be determined. Overall three pathways can be distinguished: curative, palliative and best supportive care. The difference between the pathways is the general goal. The goal of the curative pathway of course is the elimination of the cancer and full recovery of the patient.

While there is no generally valid definition of best supportive care, we use the term for patients, who receive only minimal necessary treatment to improve their quality of life. Whereas palliative patients can still undergo surgery, chemo-, immune- or radiotherapy to prolong their survival time, although the patient is very likely to die in consequence of the disease.

1.5.2 Surgery

Surgery is the first of three pillars of cancer treatment. Goal of a surgical intervention is to remove the tumor completely. This means surgery is only reasonable if a R0 resection is possible, except in palliative patients when removing the tumor only partly brings an improvement in quality of life. Whether surgery is reasonable is not only depending on the tumor size, but also on accessibility, risks and the patient's condition and the decision has to be made individually for each patient.

If a tumor is unresectable at first reduction in size and thus resectability can sometimes be achieved through neoadjuvant chemo- or radiotherapy.

The resected material is examined by surgeon and pathologist and the resection grade determined:

- R0 = no residual tumor detectable
- R1 = residual tumor microscopically detectable
- R2 = residual tumor macroscopically detectable (Hübner 2013)

1.5.2.1 Oral cavity

Carcinomas of the oropharynx can be resected at an early stage (T1 – T2) if a safety margin of 1 cm is maintained. Primary wound closure is usually possible. Depending

on the infiltration depth (more than 3 mm) neck dissection may subsequently be necessary.

If the tumor is more advanced (T3 – T4) resection is more difficult and often reconstructions are needed. In almost all cases bilateral neck dissection follows the resection (Thurnher, Grasl et al. 2011).

1.5.2.2 Nasopharynx

The nasopharynx is very difficult to access, and tumors are usually detected a late stage, which is why malignancies of the nasopharynx are commonly treated with primary chemoradiotherapy (CRT) (Thurnher, Grasl et al. 2011).

1.5.2.3 Hypopharynx/Larynx

Transoral laser-resection is possible in this area if the cancer is detected at an early stage. Nevertheless, bilateral neck dissection is necessary even for small tumors in the hypopharynx.

More advanced tumors in the hypopharynx and/or larynx often make a partial larynx resection or a complete larynx resection necessary. A permanent tracheostoma has to be created through which the patient can breathe and even learn to speak with a compensatory voice (Thurnher, Grasl et al. 2011).

1.5.2.4 Neck Dissection

Neck dissection is the surgical removal of lymph nodes in the neck area. It is necessary either because the primary tumor has already spread to the lymph nodes or in order to prevent this from happening. The human neck can contain up to 300 lymph nodes which can be divided in different surgical levels.

Level I: submandibular trigonum, can be divided in:

Level Ia: submental lymph nodes

Level Ib: submandibular lymph nodes

Level II: lymph nodes along the internal jugular vein from the hyoid bone to the carotid bifurcation

Level III: lymph nodes along the internal jugular vein from the carotid bifurcation to the omohyoid muscle

Level IV: lymph nodes along the internal jugular vein from the omohyoid muscle to the clavicle

Level V: lymph nodes of the posterior triangle of the neck

Level VI: pretracheal lymph nodes between the common carotid arteries below the hyoid bone

Apart from the radical neck dissection, there are several other types in use today in order to preserve more non-lymphatic tissue (jugular vein, m. sternocleidomastoideus, accessoric nerve) and therefore decrease postoperative complications such as nerval lesions or chyle fistula formation.

Depending on the histologic results and the tumor localization and expansion it can be necessary to resect both sides.

The different types of neck dissections are:

Radical neck dissection: levels I – V are resected, non-lymphatic tissue is not preserved

Modified radical neck dissection: levels I – V are resected, non-lymphatic tissue is preserved (if not affected by tumor)

Selective neck dissection: not all levels are resected, non-lymphatic tissue is preserved. Especially used if a kind of tumor is known to metastasize in specific levels and the neck appears clinically negative.

Lymph nodes of the sixth level are resected in cases of thyroid cancer (Thurnher, Grasl et al. 2011).

1.5.3 Chemotherapy

Chemotherapy is the second of the three pillars of cancer treatment. Cytostatics are administered to kill cancer cells by interfering in the process of cell division. This is achieved either by cytostatics bonding DNA bases covalently, fracturing strands of DNA, blocking tubulinpolymerisation or preventing repair mechanisms, to name but a few. In the process, however, healthy cells and tissue might also be damaged, depending on the spectrum of adverse effects of each individual drug, which can comprise bone marrow suppression, ulcerations of the mucous membranes, nausea, vomiting, diarrhea, loss of hair and immunosuppression (Hübner 2013).

Chemotherapy usually is administered in several cycles and can consist of one cytostatic or a combination of two or more. To maximize the effect of the therapy (and minimize toxicity and adverse effects) combinations consist of drugs with different mechanisms of action (Hübner 2013).

For treatment of malignancies in the head and neck area platinum-based chemotherapeutics (Cisplatin, Carboplatin) are the most effective ones. Platinum-based drugs interact with the DNA, causing crosslinking within the DNA strand triggering apoptosis (Lanzer 2012). Cisplatin, having the greatest therapeutic effect, also shows a wide range of side effects, such as nephrotoxicity, neurotoxicity, nausea and vomiting, ototoxicity and electrolyte disturbance (McWhinney, Goldberg et al. 2009) which is why dose reduction or switching to another drug altogether can be necessary.

Other cytostatics than Cis- or Carboplatinum used in the treatment of head and neck cancer are 5-Fluorouracil, Taxotere or Etoposid among many others. Common combinations of chemotherapeutics at LKH-Univ. Klinikum Graz are for example Cisplatin and Taxotere or Cisplatin with 5-Fluorouracil and Erbitux.

Erbitux is the trading name for Cetuximab, a chimeric monoclonal antibody inhibiting epidermal growth factor. So, it is not a chemotherapeutic drug in the proper sense but rather an immunotherapeutic drug. Adverse effects are severe infusion reactions, even anaphylactic shock and cardiac arrest although they are quite unlikely. More common side effects are rashes, pruritus, nausea and vomiting, diarrhea or obstipation and peripheral edema (Hübner 2013). The overall tolerability of immunotherapy, however, is much higher than that of chemotherapy (especially

with platinum-based cytostatics) which is why immunotherapy is not only used for the curative but also for the palliative pathway.

Not only combinations of different chemotherapeutic drugs are possible but also of chemotherapy and radiotherapy. In this case the cytostatic usually functions as radiosensitizer (Hübner 2013).

When chemotherapy is necessary additionally to surgery it is called adjuvant chemotherapy if it takes place after, and neoadjuvant if it takes place before surgery.

1.5.4 Radiotherapy

Radiation is a physical agent discovered by Wilhelm Conrad Röntgen in 1895 and plays an important role in the treatment of malignancies along with surgery and chemotherapy. The kind of radiation which is used in cancer treatment today is called ionizing radiation. This means the radiation forms ions and deposits energy in the tissues it is applied to. The cancerous cells are either killed, or their genetics are altered through the deposited energy, which can lead to the cancer cells' death, too (Baskar, Lee et al. 2012).

Healthy cells are also affected by radiation although they have better means of repairing themselves and heal more efficiently. Nevertheless, the goal is always to avoid radiation on healthy tissue as best as possible. In the head and neck area this topic is of great importance as tumor localizations often are in close proximity to delicate organs like the spinal cord, auditory and optic apparatus, vocal cords or the salivary glands. Damage to one or the other can lead to loss of function and can therefore have a severe impact on quality of life. Typical side effects are xerostomia if the parotid glands are affected or dysphagia. This is why conventional radiotherapy has been replaced by intensity-modulated radiotherapy when it comes to treating cancer in the head and neck area. Intensity-modulated radiotherapy can deliver a curative dose to the tumor-affected tissues, while sparing the healthy cells (Bhide, Newbold et al. 2012). The multicenter study PARSPORT for example showed a significant reduction of radiation-induced xerostomia for patients treated with IMRT compared with patients treated with conventional radiotherapy (Nutting, Morden et al. 2011).

1.5.5 ECOG Performance Status

In order to guarantee comparability when conducting studies for treatment of cancer standard criteria for measuring how the disease impacts a patient's daily living are used. The ECOG Performance Status is one such measurement. It describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability like walking and working. Developed by the **E**astern **C**ooperative **O**ncology **G**roup in 1982 it is still in use today and an important tool for standardization among researchers (Oken, Creech et al. 1982).

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Table 9) ECOG Performance Status Grading (Oken, Creech et al. 1982)

1.6 Tumor board

Tumor boards play an important role in the planning of individual therapy courses for patients suffering from head and neck cancer. The head and neck tumor board at the clinic for otorhinolaryngology is held at weekly intervals to discuss cases and decide on individualized therapy plans for each patient. Experts from different subspecialties, such as oncology, pathology, radiology, radiation medicine and

otorhinolaryngology are participating in the tumor board meetings. Since 2016 the subcenter “Head and Neck Tumors” is officially part of the Comprehensive Cancer Center Graz.

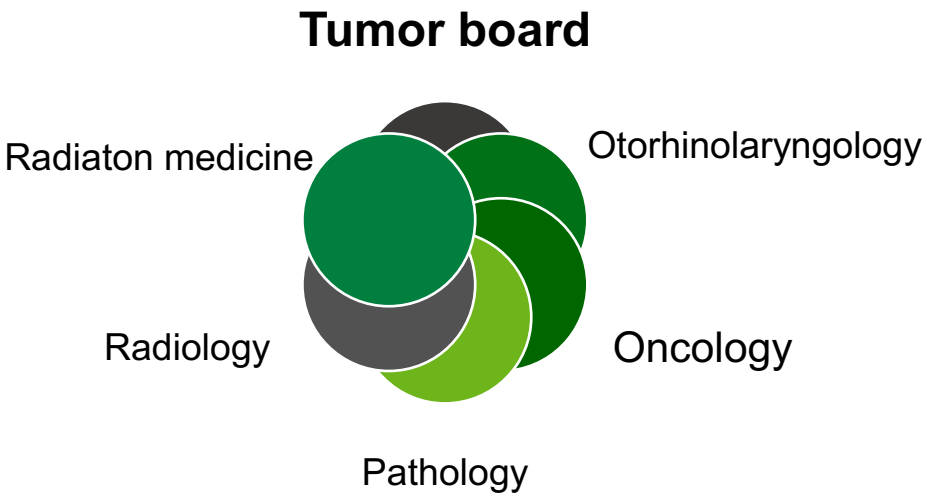

Figure 2) Pictorial representation of experts at the interdisciplinary tumor board

The result of each case discussion after looking at all available facts, is a detailed therapy suggestion. Whether surgery is possible and/or reasonable and to what extent. Whether pre- or postoperative chemotherapy, immunotherapy or radiation is indicated. Which chemotherapy, what dosage, how many cycles, and so on. The suggested therapy plan is documented in the hospital information system and later discussed with the patient, who has the last say in the therapy decision. It also happens, that the patient declines the therapy suggestion and the tumor board discusses the case again and find a different solution, more suitable to the patient’s wishes and capabilities.

1.7 Patient Management

Patients with a suspected malignancy usually present themselves at the outpatient department after seeing an established specialist, who refers them to the clinic. For the initial staging to determine the extent to which a cancer has developed imaging techniques like CT or MRI and if need be a PET-CT are used. Ideally imaging is recommended in the outpatient clinic and conducted externally in established practices. For most cancers in the field of otorhinolaryngology additionally

panendoscopy (in general anesthesia) is needed for diagnosis and staging and to rule out a second malignancy as this specific patient population are at great risk of developing more than one tumor. In order to conduct the panendoscopy the patients are asked to bring results and medical reports from external imaging and are hospitalized. Any biopsies taken during the panendoscopy are examined at the institute for pathology and as soon as the histological results are ready, and the diagnosis confirmed, the patient is presented to the tumor board.

Afterwards an appointment is scheduled for the patient at the outpatient clinic to discuss the results of the staging, the tumor board and the suggested therapy plan.

If patients are to have surgery, they have to be hospitalized again for a few days or longer, depending on the surgery and the patient's general condition.

If patients get chemotherapy it depends on the duration of the cycle whether the patient has to be hospitalized or can receive treatment in the day clinic.

Radiation takes place in the outpatient clinic at the clinic for radiation therapy. During radiation therapy the patients also have weekly appointments at the general outpatient clinic for otorhinolaryngology, where clinical checkups and lab tests are run.

Three months after the completed therapy the first re-staging including imaging, clinical examination and sonography takes place and results are discussed in detail with the patient. Afterwards clinical checkups take place every three months for two years, every six months until the completed fifth year and finally every twelve months until the completed tenth year. Additionally, imaging and re-staging is to take place once a year until the completed tenth year, ideally exactly one year after the last re-staging.

In case any of the examinations during follow up care show any suspicious changes, protocol calls for immediate re-staging, biopsies and if necessary presentation to the tumor board once again.

2 Materials and Methods

2.1 Methods

In this retrospective study, we analyzed data of patients introduced to the tumor board during the years 2014 until 2016. It was carried out at the Department of Otorhinolaryngology, Head and Neck Surgery, Medical University of Graz. Approval was given by the ethics committee of the Medical University of Graz and the study was conducted according to the declaration of Helsinki on Biomedical Research Involving Human Subjects (EK – Nb. 28-520 ex 15/16).

Inclusion criteria:

- Patient must have been presented to the head and neck tumor board for the first time.
- Confirmed diagnosis of malignancy in the head and neck area (oral cavity, oropharynx, hypopharynx, larynx, nasopharynx, nasal cavity, paranasal sinuses, tongue, lip, salivary glands, lacrimal duct/gland, soft tissue carcinoma, SCC of the skin in the head and neck area, carcinoma of unknown primary)

Exclusion criteria:

- introduced to the head and neck tumor board before
- Histological results did not confirm malignancy
- Treatment was already started by another hospital
- Wrongly introduced to tumor board regarding the primum of the tumor

Figure 3) Pictorial representation of patient selection

Between January 2014 and December 2016 (36 months) 707 patients suffering from head and neck cancer were discussed in the interdisciplinary tumor board. 151 of which were excluded. 118 due to introduction to the tumor board prior 2014, 10 because of incorrect diagnosis (no malignancy or no primary tumor in the head and neck region) and 23 were excluded due to insufficient patients medical history reports, mainly patients from external hospitals.

The remaining 556 were analyzed in this study. The data were collected from the hospital information system used at LKH-Univ. Klinikum Graz: “medocs”. Software systems as MS Excel and SPSS were used for data collection.

Variables were gathered regarding the patients’ personal information, information about the tumor and the patients’ treatment as well as the outcome in short-term follow up. The full list of variables can be found in the appendix.

2.2 Measured endpoints

2.2.1 Received primarily suggested therapy

For every patient an individual therapy plan is drawn up with consideration to the patient’s condition, age, tumor stage and survival. Our first measured endpoint was to determine whether or not the patient received the primarily suggested therapy.

2.2.2 Received full therapy

The second measured endpoint of this study was to evaluate how many patients of those, that did receive the primarily suggested therapy also received the full therapy. A full therapy was defined as the exact therapy according the primarily suggested therapy plan. Switching to a different chemotherapy, reducing the dose or number of cycles, the patient refusing surgery, or any such modifications of the therapy plan as well as termination of the therapy are considered as incomplete therapy.

If a patient did not receive the primarily suggested therapy or did not receive the full therapy, we tried to identify the reason in each case. Possible reasons were either of personal or of medical nature, e.g. patient refusing surgery, chemotherapy or

radiation or deterioration of the patient's general condition, low counts of leucocytes and/or platelets, allergic reactions to the chemo-/immunotherapy and strong adverse effects, such as labyrinthine deafness.

2.3 Focus

The overall focus of this thesis lies on the quality management of the head and neck tumor board at LKH-Univ. Klinikum Graz. We concentrated on the primary therapy suggestions for the main groups of tumor patients which we defined as patients with carcinomas of the larynx and hypopharynx, oral cavity and oropharynx, nasopharynx, nasal cavity and paranasal sinuses, salivary glands and CUP. Primarily suggested therapy plans were assessed and compared to each other. Practicability was evaluated, and potential problems identified. Further we focused on gender differences.

Smaller groups, such as soft tissue carcinomas, carcinomas of the lacrimal gland/duct or lymphomas will not be discussed to a great extent due to reasons of small case numbers and comparability as well as to keep this thesis reasonably short and still be able to go into detail for the main groups.

SCCs of the skin will not be discussed either as many cases of SCCs of the skin are treated in departments other than the department of otorhinolaryngology (e.g. dermatology, urology, gynecology, …) and we cannot provide complete case numbers or enough information on externally treated SCCs of the skin to include this group in the discussion.

2.4 Statistical Analyses

Primary endpoints were receiving of suggested therapy, fully received suggested therapy plan and overall survival during a mean follow-up of 21.1 ± 11 months. Assessed variables were Patient ID, date of birth, postal code of the place of residence, sex, date of death, date of first diagnosis, date of first tumor board council meeting, tumor localization, tumor side, TNM stage, histological entity, keratotic, p16, comorbidities (pulmonological, cardiac, renal, liver, psychological, neurological, hematological, others), primary path of suggested therapy (curative,

palliative, best supportive care), suggested therapy (surgery, radiation, chemotherapy), received therapy.

Data analysis was performed using SPSS software (version 25.0; IBM SPSS Statistics). Data are described as medians with ranges or means with standard deviations, as appropriate. Comparisons of continuous or categorical variables were performed with Student's t-test or Mann–Whitney-U test, and Chi-squared tests or Fisher exact test, as appropriate. Statistical significance was set at P=0.05. Comparisons were made between subgroups. Kaplan-Meier analysis was used to estimate overall survival. Significances are identified by log-rank test. Cox - proportional hazard modelling was used to analyses risk-predicting interruption of therapy and death.

3 Results

3.1 Patients

During 2014 and 2016 a total of 707 patients have been introduced to the interdisciplinary tumor board for head and neck tumors at LKH-Univ. Klinikum Graz. Patients presented to the head and neck tumor board for the first time were included to the study. After excluding 151 patients following exclusion criteria, a set of 556 patients build the cohort for further analysis. About three quarters of patients were male (N=415; 74,6%,) and one quarter female (N=141; 25,4%).

More than half of the patients (52.9%) had ECOG performance status 0, about one third (32%) ECOG 1, 10.1% ECOG 2, 3.2% ECOG 3 and 1.3% ECOG 4. There was no significant difference of ECOG distribution among gender.

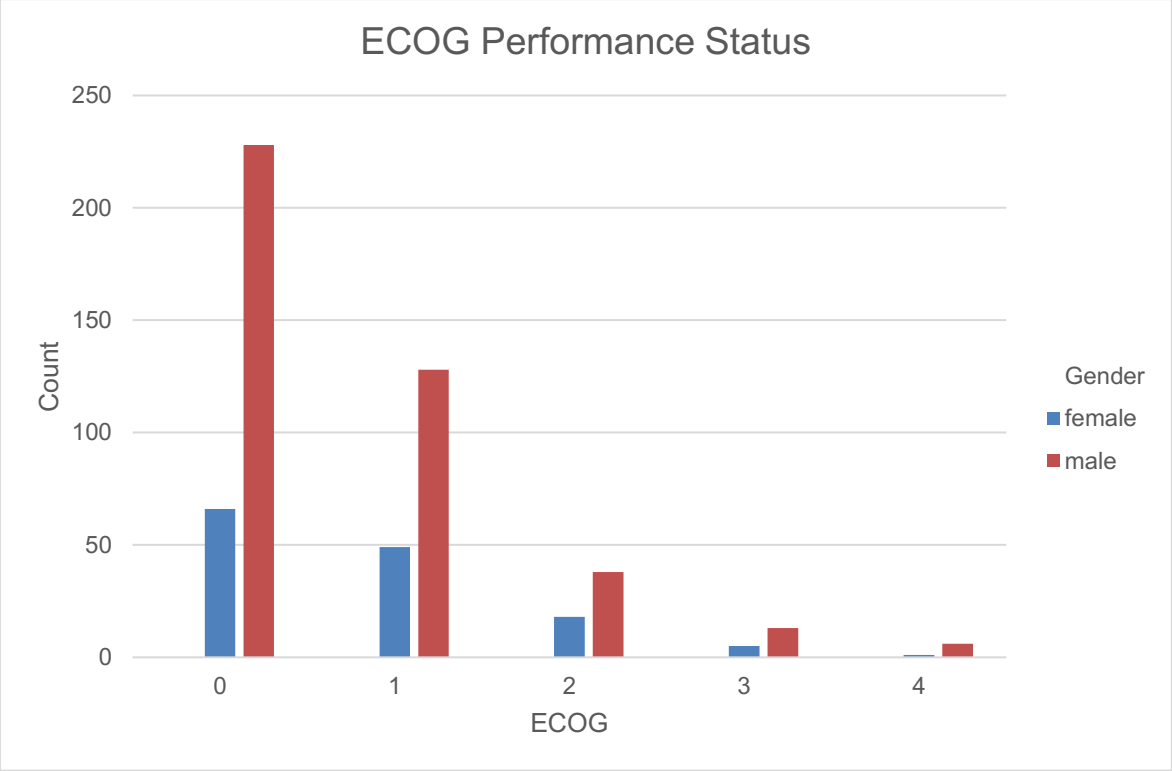

Figure 4) ECOG Performance Status with regard to sex in frequencies

3.2 Tumor localization

Most patients (N=130; 23.4%) had a carcinoma of the oropharynx followed by malignancies of the larynx (N=105; 18.9%) and the oral cavity (N=103; 185%). The remaining groups were a lot smaller: There were 35 patients (6.3%) with a tumor of

the skin, 31 (5.6%) with a malignancy in the paranasal sinuses, 31 (5.6%) with a tumor in the hypopharynx, 25 (4.5%) with a tumor of the parotid gland, 25 (4.5%) with a carcinoma of unknown primary, 17 (3.1%) with a tumor in the nasal cavity, 15 (2.7%) with a tumor in the nasopharynx, 6 (1.1%) with tumors of the soft tissue, 4 (0.4%) with a tumor in the submandibular glands, 3 (0.3%) with a malignancy in the lacrimal duct and 27 others.

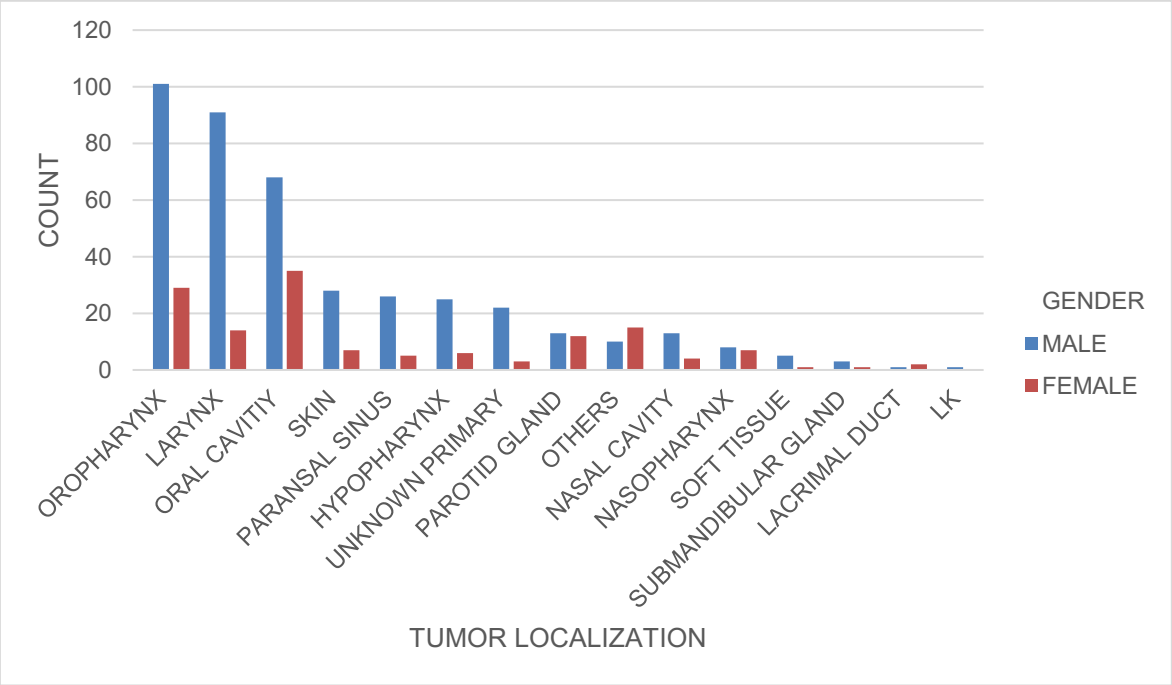

Figure 5) Distribution of tumor localizations with regard to sex in frequencies

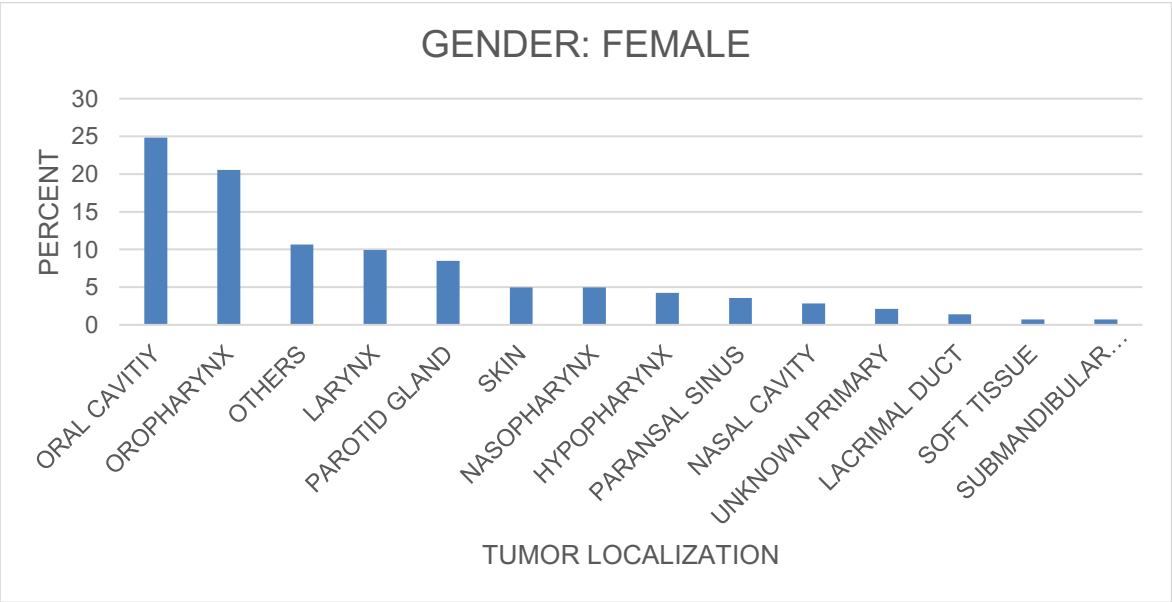

Figure 6) Distribution of tumor localizations in women in percentage

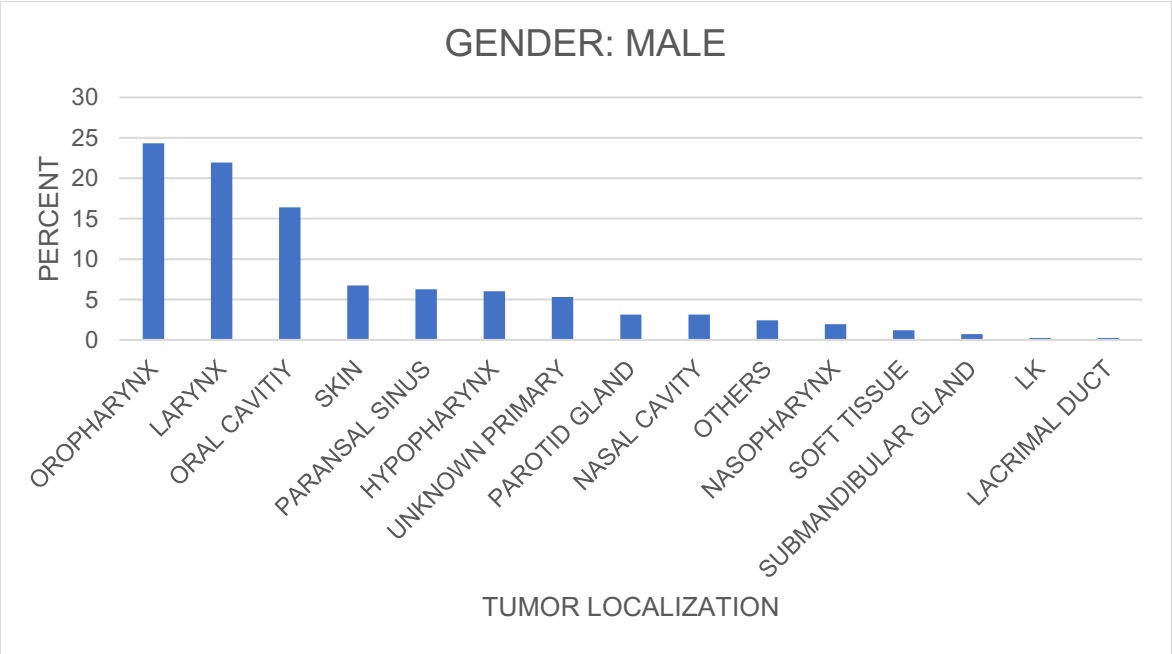

Figure 7) Distribution of tumor localizations in men in percentage

3.3 TNM Staging

A set of 248 patients (45.1%) already had an advanced stage of the tumor (T3 or T4) when they presented at the department of otorhinolaryngology at LKH-Univ. Klinikum Graz, there was no significant difference in distribution of tumor size between male and female.

Locoregional lymph node staging could be assessed in 496 (89.2%) patients and locoregional lymph node metastases could be clinically identified in 47.1 % (f: N=55; 48.2% vs. m: N=197; 51.6%, p=0,062) of the patients. Distant metastases could only be detected in 8.7% (f: N=8; 7.2% vs. m: N=32; 9.2%; p=0,513) despite high tumor stages.

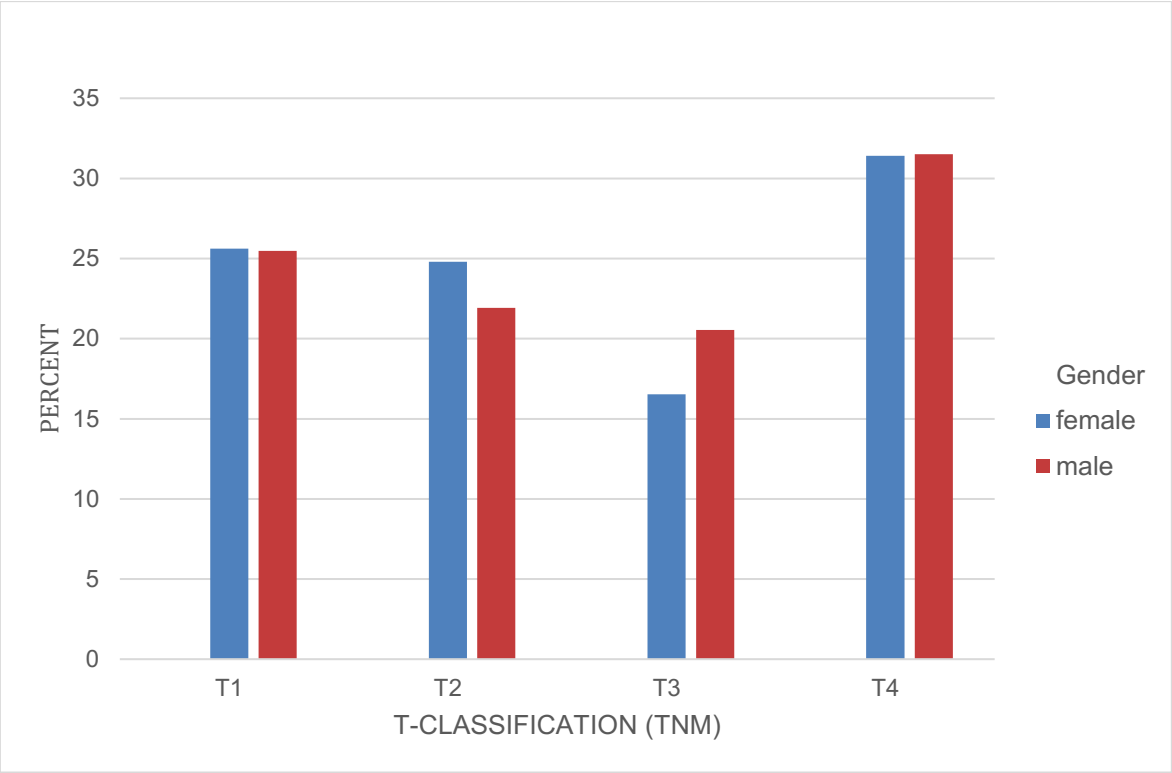

Figure 8) T – classification with regard to sex in percentage

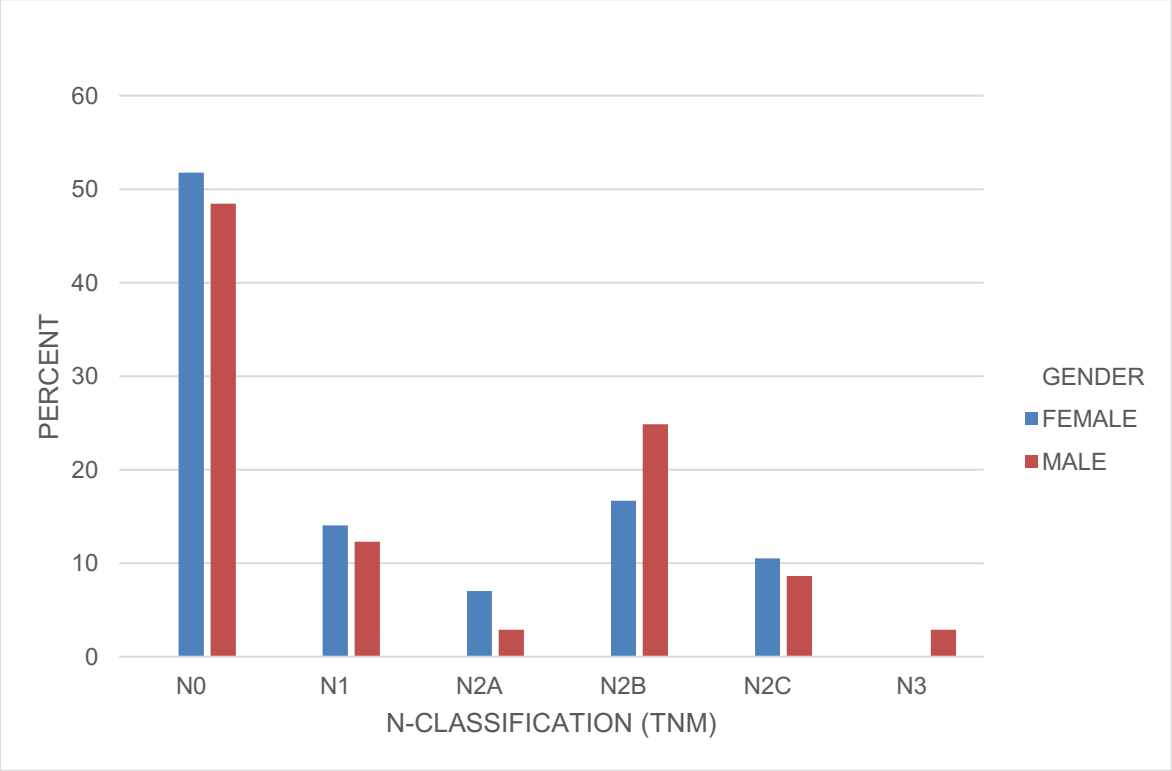

Figure 9) N – classification with regard to sex in percentage

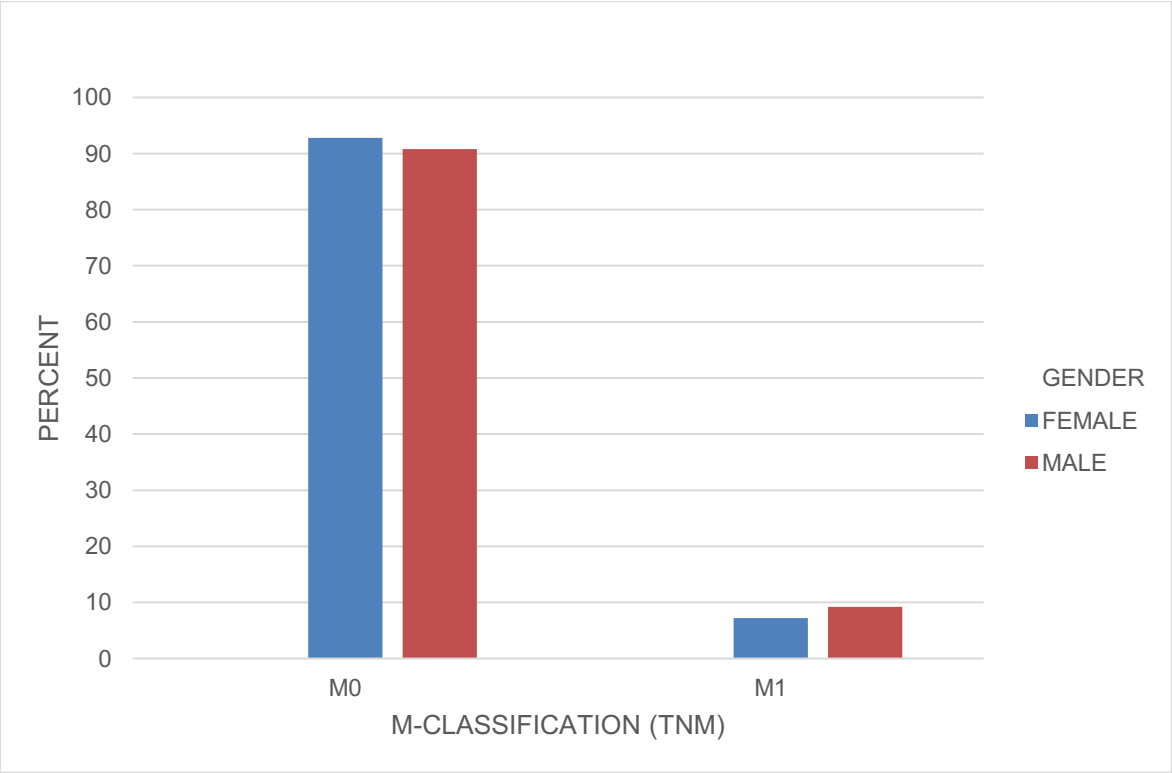

Figure 10) M – classification with regard to sex in percentage

3.4 Therapy

3.4.1 Pathway

Most patients (N=450; 80.6%) were categorized into the curative pathway and only 59 (10.6%) patients received palliative treatment. Best supportive care pathway without tumor specific treatment was chosen for 47 (8.5%) patients.

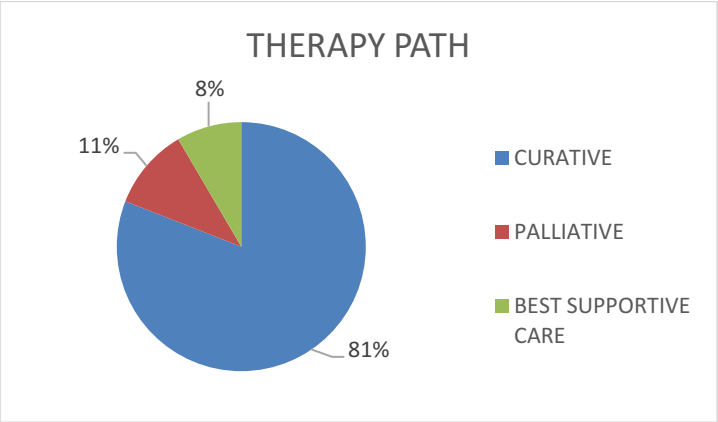

Figure 11) Pathway chosen by the interdisciplinary tumor board

3.4.2 Primarily Suggested Therapy Plan

The therapy plan suggested primarily by the interdisciplinary head and neck tumor board is lined out in figure 12. Surgery followed by chemotherapy and/or radiotherapy was suggested for 154 (27.7%) patients. Chemoradiotherapy without surgery was recommended in 24.8%. Start of suggested therapy was possible in 519 (93.3%) patients and 411 (73.9%) completed their full therapy. External hospitals managed the treatment phase of 3.8% (N=21) where we have no valid data to proof fully completed therapy.

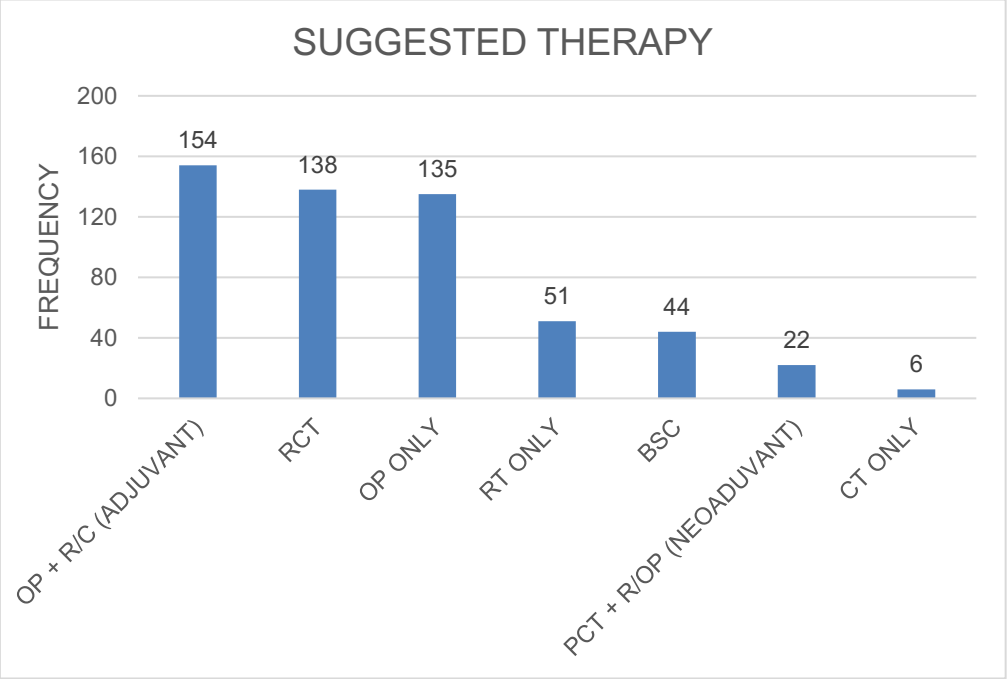

Figure 12) Primarily by the interdisciplinary tumor board suggested therapy plan

3.4.3 Surgery

A set of 291 (52.3%) patients underwent surgery. The histological findings showed R0-resection in 82.8% (f: N=63; 81.8% vs m: N=178; 83.2%, P=ns). R1-resection in 13% (f: N=10; 13.0% vs m: N=28; 13.1%, P=ns), and 4% had neck dissection only, a lymph node extirpation or surgery in order to reduce the size of the tumor (tumor debulking).

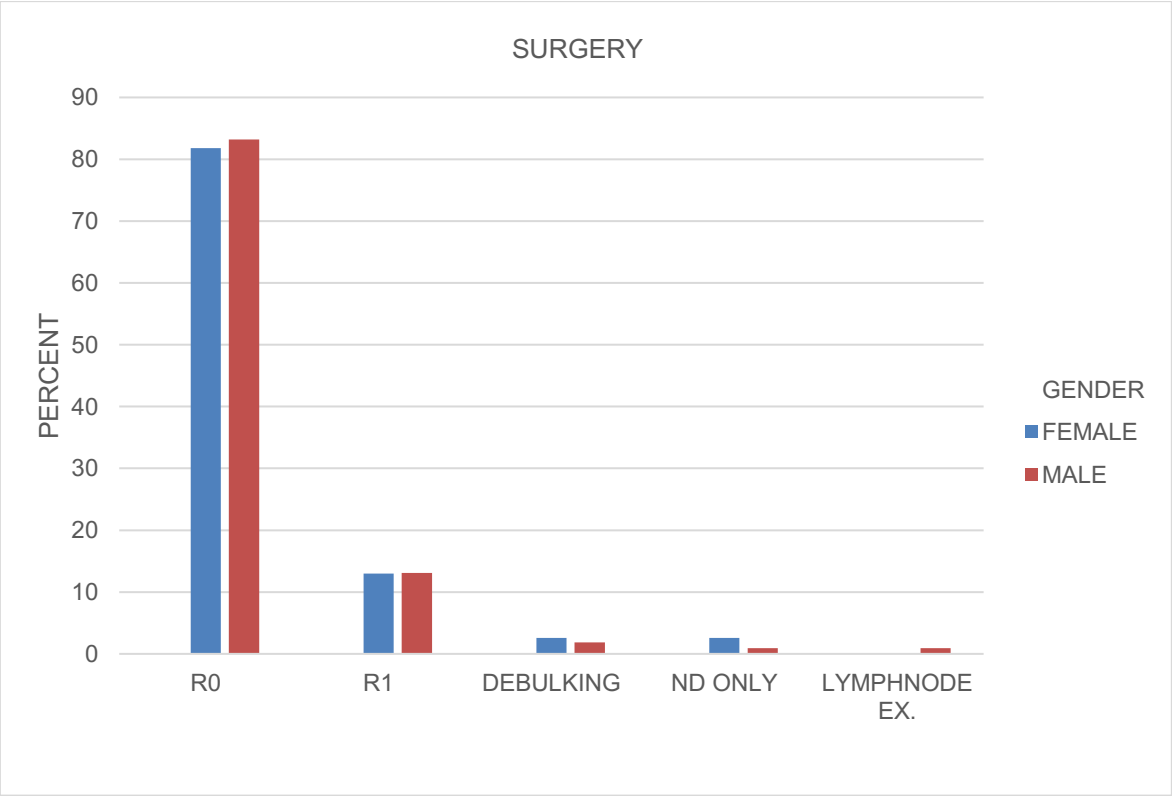

Figure 13) Kind of surgical resection with regard to sex in percentage

Patients who underwent surgery also received neck dissection in 54,6%. ipsilateral neck dissections were performed in 69.1% and bilateral in 30.8%. There were no significant differences between men and women.

47.4% of the patients did not have surgery at all, mostly due to tumor size. Other reasons were comorbidities (25.9%; f: 21.2% vs. m: 27.6%), age 5.1% (f: 9.6% vs. m: 3.4%) or the patient not wanting surgery 13.2% (f: 7% vs. m: 15.2%). There was no significant difference between men and women, but women were rejected for surgery mainly regarding their age and tumor size. Compared to men, women with

head and neck cancer showed a lower rate in comorbidities and lower rate of refusal to surgery.

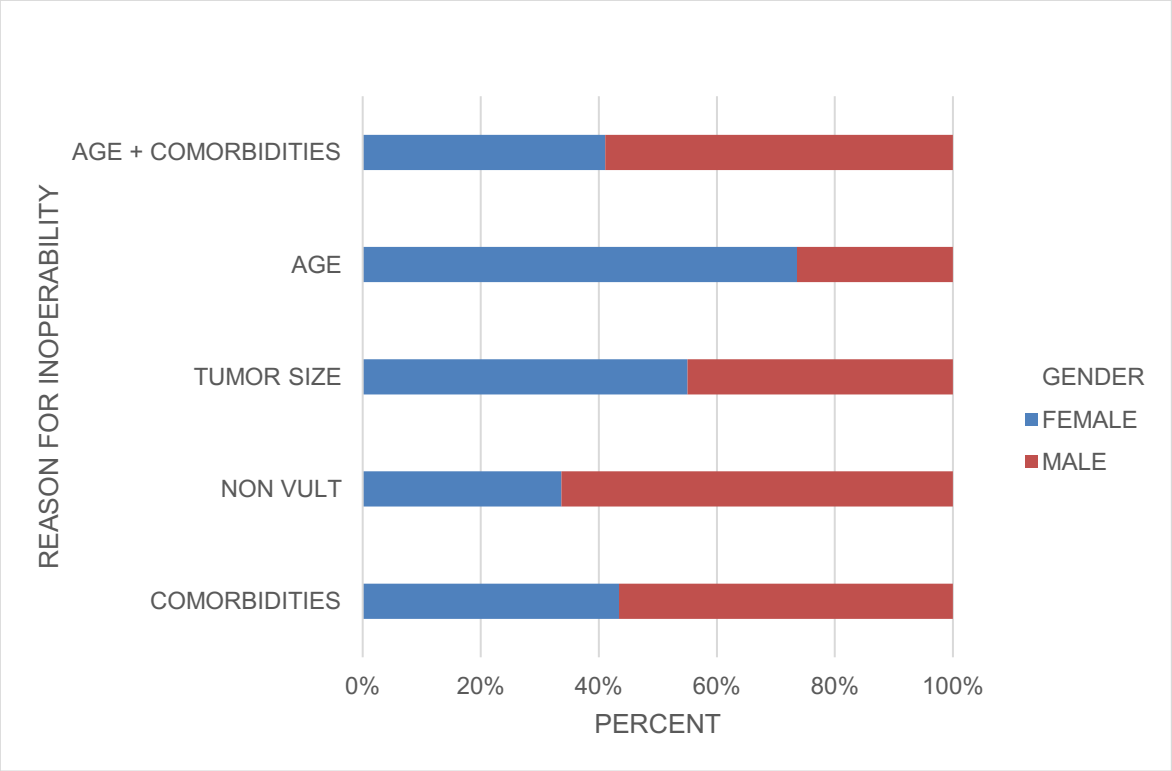

Figure 14) Reasons for inoperability with regard to sex in percentage

3.4.4 Chemotherapy

Out of 556 patients 211 (37.9%) were suggested to receive chemotherapy, a set of 186 (86.5%) finally started. By far the most of them received chemotherapy with cisplatin (72.2%), either as monotherapy (53%) or in combination with other chemotherapeutics (19.2%). In 14 (2.5%) cases cisplatin had to be replaced by carboplatin during therapy, mostly due to hypacusis (N=8) and reduced renal function (N=3).

Carboplatin was administered in 5.9% as monotherapy and in 13.4% in combination with other drugs. 10.8% received a combination of Docetaxel, Cisplatin and 5-Fluoruracil (TCF) and 5.9% received chemotherapy according to the Calais scheme. Combinations of Taxotere/Cisplatin and Carboplatin/AUC2 were given to 7 (3.8%) patients each. In 17.1% other chemotherapeutics and/or combinations were administered.

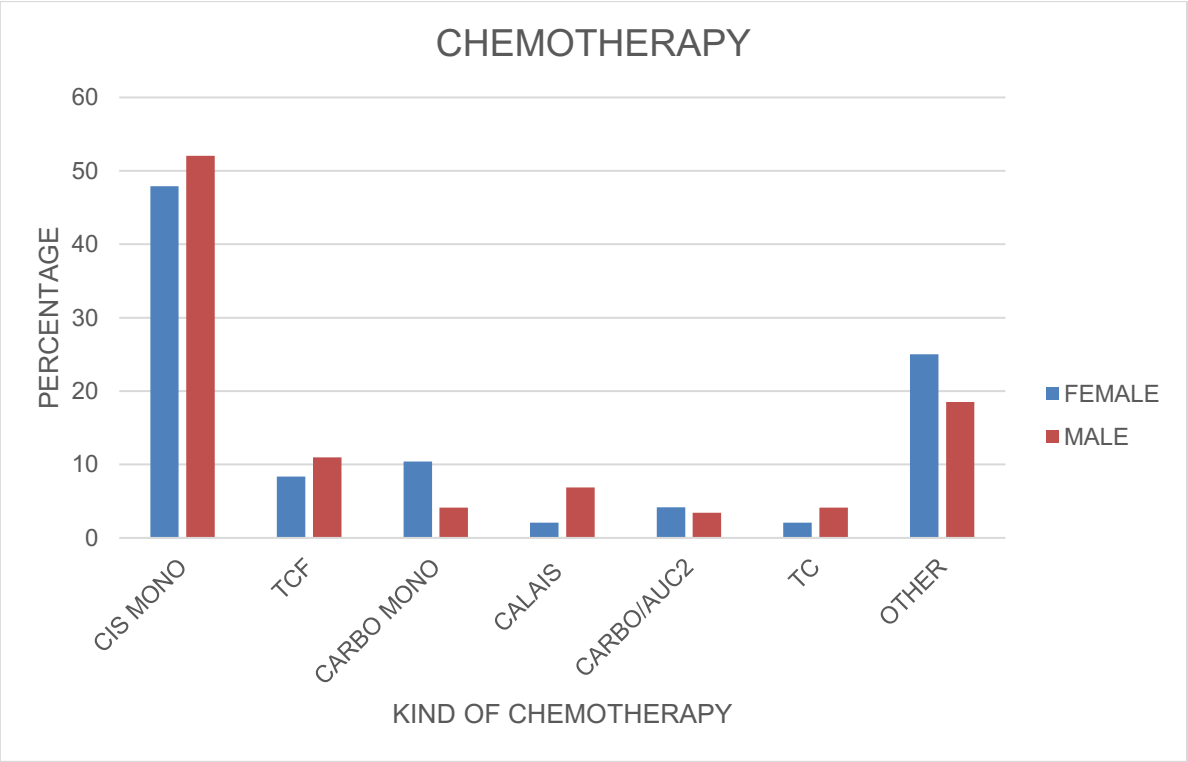

Figure 15) Kind of chemotherapeutics suggested, with regard to sex in percentage

36% of all chemotherapies were terminated prematurely, the most common reason being low leukocyte counts (29.9%), followed by deterioration of the general condition (20.9%).

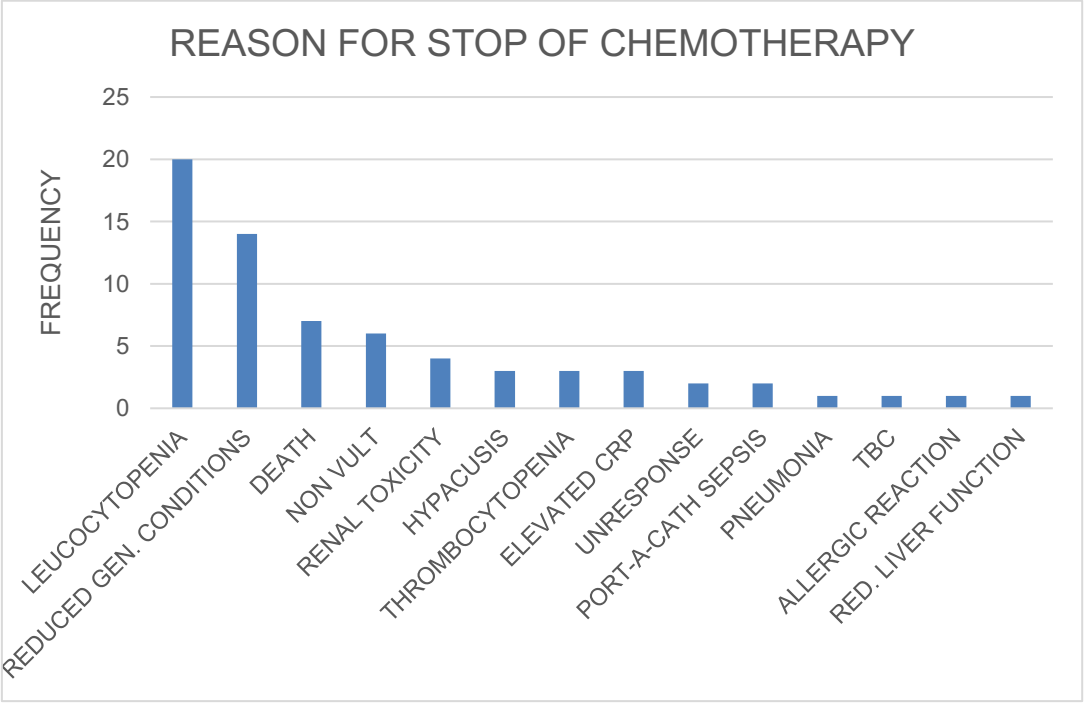

Figure 16) Reasons for terminating chemotherapy in frequencies

3.4.5 Radiotherapy

Almost two thirds, 364 (65.5%) patients, were recommended to undergo radiotherapy, 346 (95.1%) of those finally started radiotherapy. In 38 (11%; f: N=15; 19% vs. m: N=23; 8.6%, p=0.01) cases radiotherapy was terminated, significantly more often in women. Reasons were 1) refusal to continue therapy (N=21, 55.3% f: N=8; 57.1% vs. m: N=13; 54.2%), 2) deterioration of general condition (N=9, 23.7% f: N=2; 14.3% vs. m: N=7; 29.2%), death of the patient (N=6, 15.8% f: N=4; 28.6% vs. m: N=2; 33.3%), or a too long latency between chemotherapy and radiation (m: N=1, 2.6%).

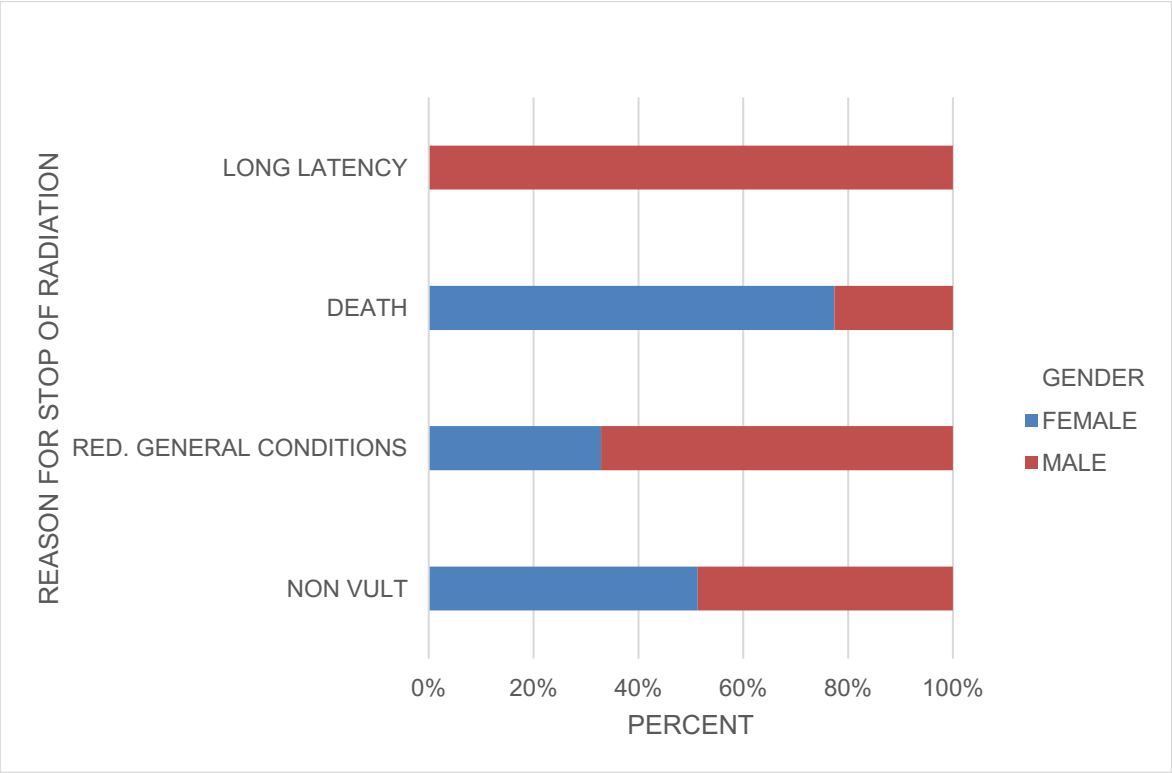

Figure 17) Reasons for terminating radiotherapy with regard to sex in percentage

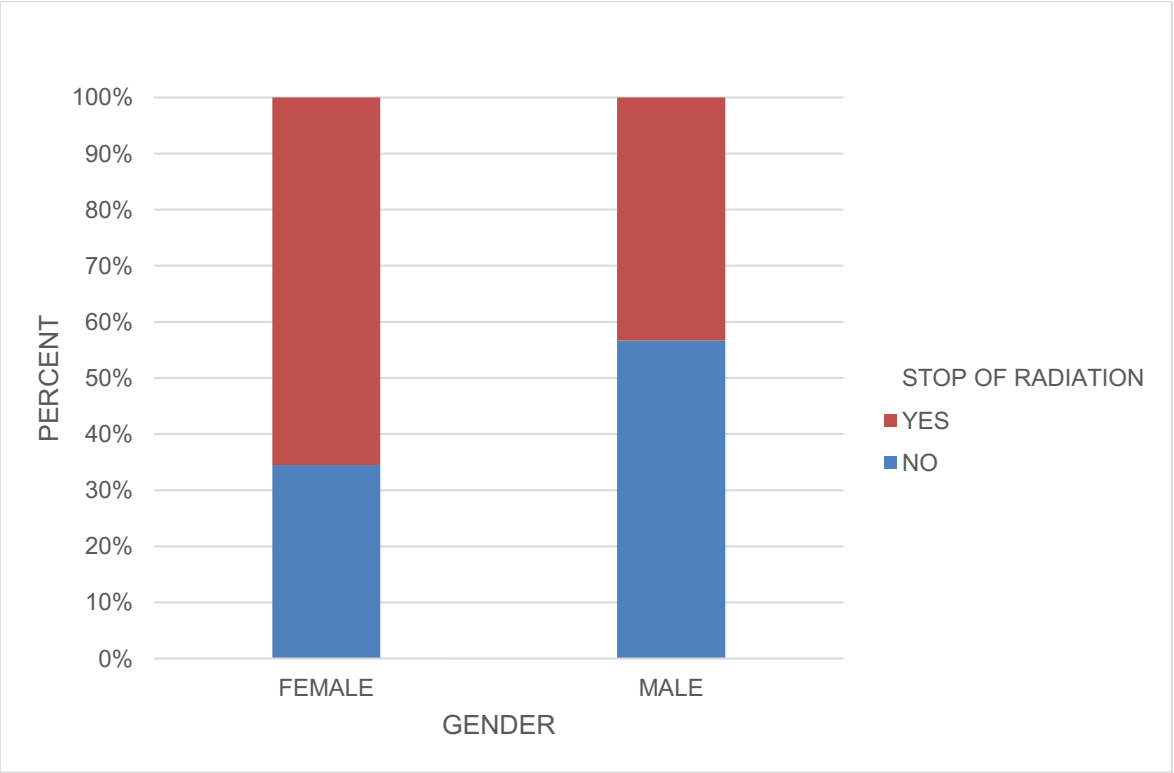

Figure 18) Gender differences regarding termination of radiotherapy

3.4.6 Immunotherapy

For 35 patients (6.3%) immunotherapy was suggested. Termination of the immunotherapy was necessary in 10 cases (28.6%). 4 patients had an allergic reaction to the administered drugs, 3 patients showed a deterioration of general condition, 2 patients died during immunotherapy, 1 patient did not want to continue therapy.

3.5 Overall Survival

In the total cohort the mean overall survival was 38.918 months, with August 4th, 2017 as cutoff point. The mean overall survival in men was 38.871 months, while in women it was 39.036 months. There was no statistical significance in overall survival between men and women.

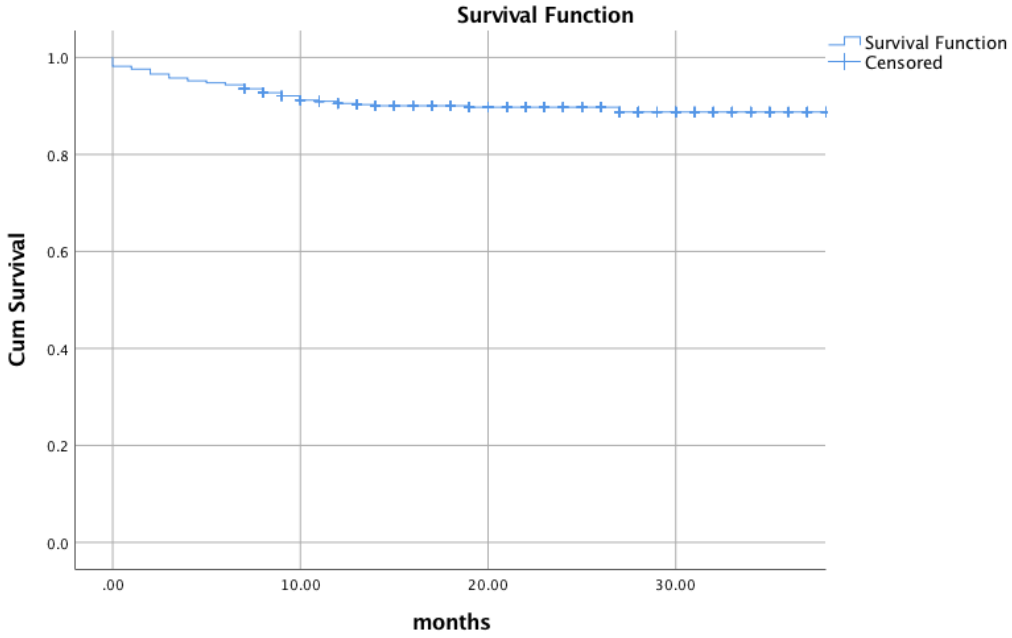

Figure 19) Kaplan-Meier curve, showing overall survival

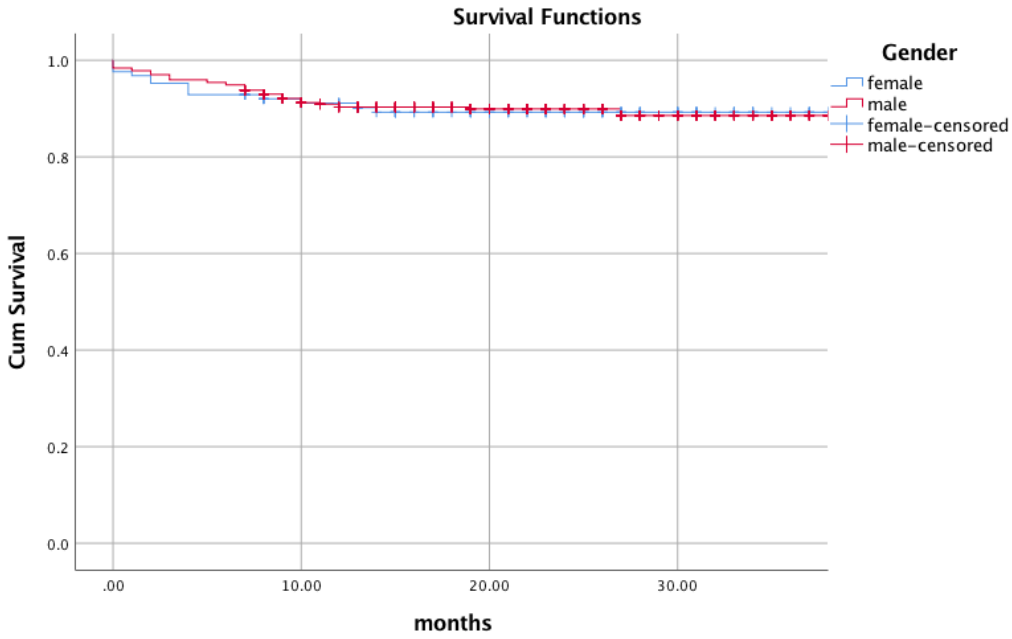

Figure 20) Kaplan-Meier curve, showing no statistically significant difference in overall survival in men or women

To estimate survival for patients with termination during treatment we excluded patients that died within the first 2 months after diagnosis due to bias effect. The survival in the terminated therapy arm was slightly lower than the overall survival with P=0.064 only just above significance level.

	Mean[a]			
			95% Confidence Interval	
Therapy completed	Estimate	Std. Error	Lower Bound	Upper Bound
no	37.161	1.305	34.603	39.719
yes	39.364	.488	38.406	40.321
Overall	38.918	.473	37.991	39.844

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.443	1	.064
Breslow (Generalized Wilcoxon)	4.480	1	.034
Tarone-Ware	4.024	1	.045

Test of equality of survival distributions for the different levels of Therapy completed.

Figure 21) Statistical analyses to compare overall survival between patients who completed therapy and patients who terminated therapy

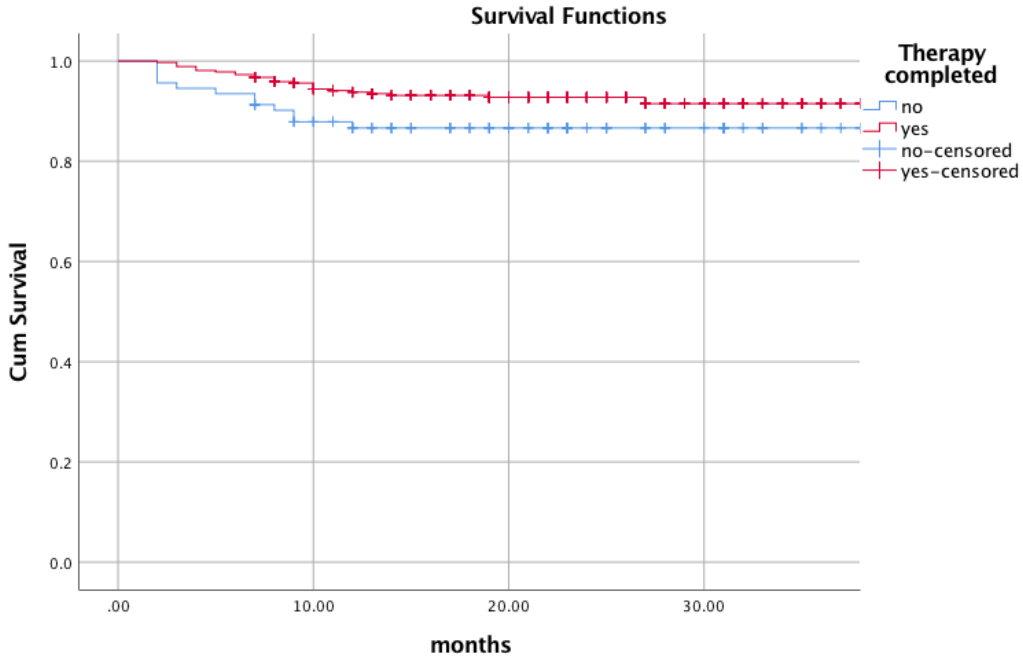

Figure 22) Kaplan-Meier curve, showing no statistically significant difference in overall survival in patients with completed and terminated therapy

Dividing the patients in subgroups regarding sex and completion of treatment, similar results can be found. In the terminated therapy arm survival was again slightly lower than the overall survival with P=0.062.

		Mean[a]			
				95% Confidence Interval	
Gender	Therapy completed	Estimate	Std. Error	Lower Bound	Upper Bound
female	no	36.888	2.751	31.496	42.280
	yes	39.596	.949	37.737	41.456
	Overall	39.036	.948	37.177	40.895
male	no	37.246	1.481	34.343	40.149
	yes	39.283	.570	38.165	40.400
	Overall	38.871	.546	37.800	39.942
Overall	Overall	38.918	.473	37.991	39.844

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons[a]

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	3.490	1	.062
Breslow (Generalized Wilcoxon)	3.705	1	.054
Tarone-Ware	3.705	1	.054

Test of equality of survival distributions for the different levels of Therapy completed.

a. Adjusted for Gender.

Figure 23) Statistical analyses to compare overall survival between men and women who completed therapy and men and women who terminated therapy

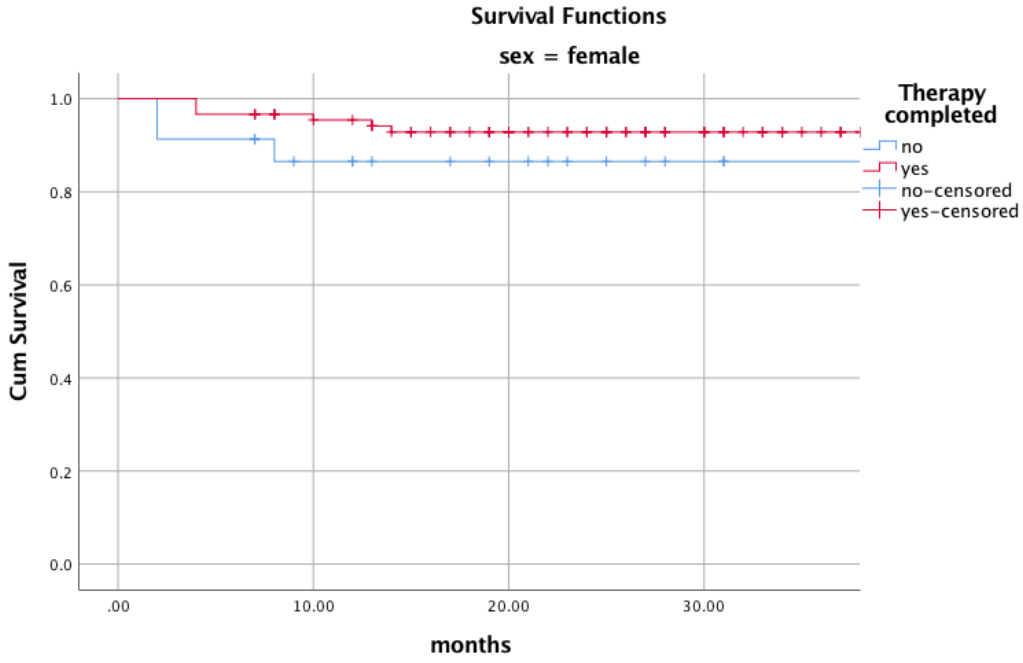

Figure 24) Kaplan-Meier curve, showing no statistically significant difference in overall survival in men with completed and terminated therapy

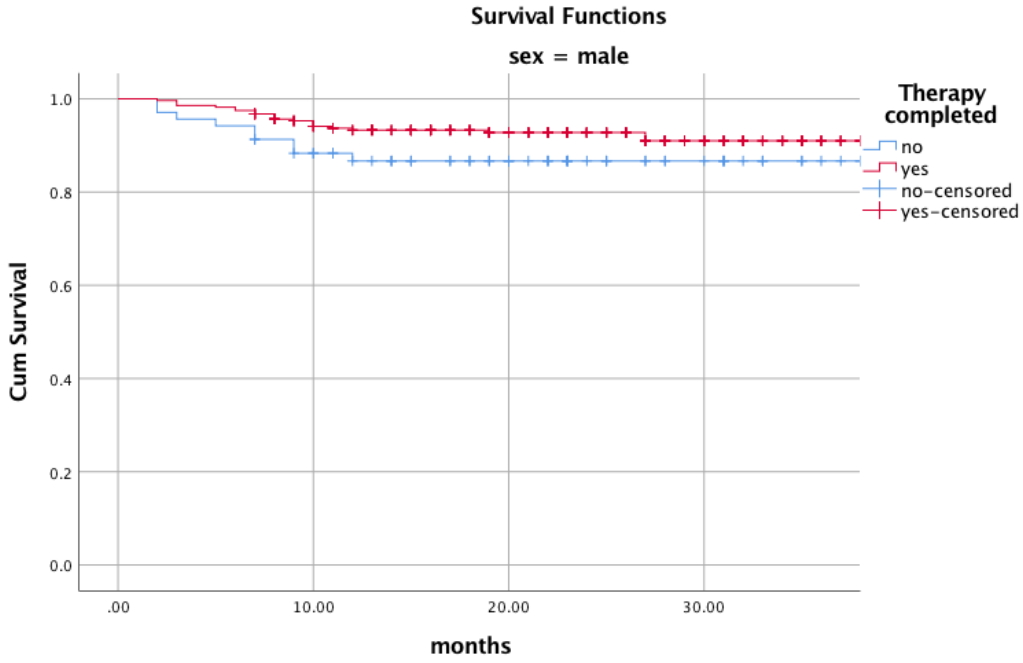

Figure 25) Kaplan-Meier curve, showing no statistically significant difference in overall survival in men with completed and terminated therapy

3.5 Measured endpoints

3.5.1 Primarily Suggested Therapy and full therapy

Our retrospective data analyses showed satisfactory results. 93% of all included patients, 523, received the primarily suggested therapy. In 7% there is no documentation of any therapy either because the patient refused therapy, the patient died before beginning the therapy, or because the patient was treated externally, in which case no data was available.

Start of suggested therapy by the head and neck tumor board was possible in 519 (93.3%) patients and 411 (73.9%) patients completed the full therapy. External hospitals managed the treatment phase of 3.8% (N=21) patients where we have no valid data to proof fully completed therapy.

4 Discussion

A multidisciplinary approach especially to oncologic patients is becoming more prevalent in modern medicine and is even considered a standard of care in many cancer subspecialties (Sidhom, Poulsen 2006). Kimmeyer, Kurzweg et al. conducted a study in German-speaking countries (Germany, Austria and German-speaking parts of Switzerland) to describe the current treatment landscape and infrastructure regarding the treatment of head and neck squamous cell carcinomas. They found that in 98.4% of the participating 62 treatment centers a multidisciplinary tumor board was existent (Kimmeyer, Kurzweg et al. 2016).

Many studies have shown that involving a multidisciplinary tumor board in the process of decision making benefits patient outcomes (Wright, De Vito et al. 2007, Westin, Stalfors 2008, Wheless, McKinney et al. 2010). Westin and Stalfors even found that the multidisciplinary team was able to minimize complications and had a beneficial influence on cost effectiveness.

4.1 Therapy

Out of the available therapy options radiotherapy was by far most oftenly recommended. For almost two thirds of all patients the tumor board suggested radiotherapy and most of them subsequently started radiotherapy either as mere radiation therapy or as CRT. Radiation as one of the key options in the treatment of head and neck cancers can also be observed in literature. Nguyen, Vos et al. for example found that out of 225 patients with head and neck cancer 213 were recommended to undergo either radiation therapy or chemoradiation (Nguyen, Vos et al. 2008).

Compared to chemotherapy and immunotherapy, radiation therapy seems to be more tolerable for patients. While 36% of chemotherapies and 28.6% of immunotherapies had to be terminated, only 11% of radiotherapies were terminated early. This might have to do with the fact that patients have weekly checkups at the general outpatient clinic of the clinic for otorhinolaryngology where potential side effects of the radiotherapy, such as mucositis or dermatitis are explained to the patients, can be detected and treated immediately. Additionally, the patients feel

that they are cared for much better, which can positively affect their psychological and mental health.

Unfortunately, comparable studies on this topic can rarely be found in literature. Nevertheless, numbers regarding the early termination of radiation therapy vary. George, Yom et al. compared radiation treatment in academic and non-academic medical centers in the US. They showed that patients treated at non-academic medical centers were less likely to receive the full course of radiotherapy. 25.4% of radiation therapies had to be terminated at non-academic and only 1.1% at academic medical centers (George, Yom et al. 2013). As a possible cause for the great difference they mention broad demographic and clinicopathologic differences. Sommat, Yit et al. also had very high numbers regarding completion of the therapy course. Out of 185 patients with nasopharyngeal carcinoma as many as 180 (97.3%) received the full radiation therapy. (Sommat, Yit et al. 2018).

4.2 Gender Differences

The significant difference between men and women is another interesting aspect. While only 8.6% of men did not receive the full course of radiation therapy, the number for women was as high as 19%. Reasons for termination were quite similar in both genders: mostly refusal to continue therapy, followed by deterioration of general condition, death of the patient or a too long latency between chemotherapy and radiation. The fact that women are more likely to discontinue, or interrupt radiotherapy can be observed in other studies, as well. For example, in the study of Lebwohl et al. They conducted a study in New York in two medical centers regarding radiotherapy of newly diagnosed rectal cancers and found that 5% of the patients discontinued radiation therapy and 100% of them were female. Female gender was also strongly associated with treatment interruption. Reasons for both phenomenona were unknown. (Lebwohl, Ballas et al. 2010). Similar results were found by Mohanti et al., who analyzed patient management, treatment compliance and outcome of head and neck cancer patients at a regional cancer center in India. Again, women were significantly less likely to comply to therapy decisions (Mohanti, Nachiappan et al. 2007). As mentioned above the reasons for this phenomenon are obscure. One possible explanation might be that women commonly have a better

awareness of their body and are therefore more likely to experience adverse reactions. Generally, females also attach greater importance to mental health issues than males and might profit from psychological support during the course of therapy.

4.3 Follow Up Care

Another important aspect when talking about cancer treatment is the follow up care. At the clinic for otorhinolaryngology at the LKH-Univ. Klinikum Graz tumor board patients have scheduled short-term checkups after completing the therapy and are continuously monitored including imaging once a year until the completed tenth year after therapy at the outpatient clinic. Thus, in case of recurrence of the tumor, it is caught early and can be treated immediately. This is crucial as described by de Visscher et al. Although the study has been published in 1994, it is still relevant. They found that the mean survival after detection locoregional recurrence, distant metastases or second primary tumors with routine follow-up was significantly better than with self-referral (58 vs 32 months, respectively) (de Visscher, Manni 1994). 10 years of regularly scheduled follow up at the clinic for otorhinolaryngology is quite a long time and a great success compared to many others according to literature. Xiang et al. had a median follow up time of only 3.5 years for surviving patients in their study (Xiang, Holsinger et al. 2018), while the current common practice in the UK for example is five years of surveillance (Simcock, Simo 2016).

4.4 Conclusion

Multidisciplinary tumor boards have become indispensable when making therapy decisions for head and neck cancer patients. Our retrospective data analyses of the tumor board patient data showed satisfactory results. 93% of all included patients received the primarily suggested therapy and 73.9% completed therapy according to the treatment plan without any changes. Radiation therapy seems to be the most tolerable therapy option as only 11% of radiotherapies were terminated early. Women were significantly more likely to terminate radiation than men. The reasons for this should be further investigated. In terms of follow up care the clinic for

otorhinolaryngology of the LKH-Univ. Klinikum Graz is ahead of common standards worldwide with 10 years of follow up care with yearly imaging.

4.5 Limitations

Limitations in our study include that data regarding the tumor board and patient history is not yet standardized. A lot of data is available in the hospital information system, but mostly not in the form of standardized forms, but for example as doctor's letters which are written freely. Additionally, no standardized questionnaire regarding the patients' quality of life (e.g. SF-36) was used, which is why no valid statement can be made on this topic. Closely related to quality of life is the psychological aspect. Unfortunately, the psychological problems were not assessed at all in the course of this study due to missing information on that part. For the future quality of life and psychological health assessments should be included in some form or other in the tumor board, as both are essential for successful treatment.

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Appendix

Full list of assessed variables

Variable	Label	Measurement Level
Pat_Name	Patient name	Nominal
Tumorboard_ID	<none>	Nominal
Pat_ID	<none>	Nominal
GD	<none>	Nominal
Geb_Datum	<none>	Scale
Herkunft	<none>	Nominal
Herkunft_code	<none>	Nominal
Herkunft_KfZ	<none>	Nominal
death	<none>	Nominal
@1st_TB	First presentation	Scale
@1415_TB	First presentation (2014-2016)	Scale
age_1stTB	Age at first presentation	Scale
age_1415TB	Age at first presentation (2014-2016)	Scale
Group_year_1stTB	First presentation	Nominal
Group_yes_14_15	All presentations 2014-15	Nominal
Group	Group	Nominal
sex	Gender	Nominal

Fehlvor	Wrongly introduced	Nominal
PrimärTumor	Primary tumor	Nominal
T_loc	Tumor localization	Nominal
T_side	Tumor side	Nominal
StadiumPrimärstaging	Primary stage	Nominal
T_class	T-Classification (TNM)	Nominal
N_class	N-Classification (TNM)	Nominal
M_class	M-Classification (TNM)	Nominal
I_Stad	Tumor Staging	Nominal
Histo	Histology	Nominal
H_kind	Histology	Scale
EBV	<none>	Nominal
p16	p16	Nominal
keratotic	Keratosis	Nominal
HPV	<none>	Nominal
Diff_grade	Grading	Nominal
ECOG	<none>	Nominal
Path_A	Path	Nominal
Immuno	Immunotherapy in primary suggestion	Nominal

Prim.Therapievorschlag	Primarily suggested therapy	Nominal
Prim_Ther	Primarily suggested therapy	Nominal
RADIATIOimPrimärvorschlag	Radiotherapy in primary suggestion	Nominal
RAD	Radiation	Nominal
RAD_stop	Stop of radiation	Nominal
RAD_reason	Reason for stop of radiation	Nominal
Begleiterkrankungen	Other diseases	Nominal
died	died	Nominal
today_cutoff	<none>	Scale
age_death	Age at death	Nominal
primäreTherapieerhalten	sugg. therapy started	Nominal
vollständig	Therapy completed	Nominal
wenn_nicht_Grund	reason for change in therapy	Nominal
Prim_Vorschlag	Suggested Therapy	Nominal
CHTHImmuntherapieimPrimärvorschlag	CHTH/Immunotherapy in primary suggestion	Nominal
CHTH_only	<none>	Nominal

CHEMO_rec	Any chemotherapy received	Nominal
CHEMO_kind	Kind of chemotherapy	Scale
CHEMO_stop	Stop of chemotherapy	Nominal
CHEMO_reason	Reason for stop of chemotherapy	Scale
CHEMO_change	<none>	Nominal
CHEMO_Umstellungauf	Change in chemotherapy	Nominal
CHEMO_Umstellung_reason	Reason for change in chemotherapy	Nominal
IMMUN	Immunotherapy	Nominal
IMMUN_stop	Stop of immunotherapy	Nominal
IMMUN_reason	Reason for stop in Immunotherapy	Nominal
OP	<none>	Nominal
OP_poss	Operability	Nominal
OP_date	<none>	Scale
OP_kind	Kind of surgery	Nominal

OP_nonposs	Reason for inoperability	Nominal
Re_OP	Re-OP	Nominal
Re_OP_kind	Kind der re-OP	Nominal
OP_A	Surgery	Nominal
Neck	Neck dissection	Nominal
Neck_posLN	Lymphnode metastasis	Nominal
Sur_event	Cumulative survival	Nominal
Sur_dur1	months	Scale