

ROBOTIC SURGERY OF THE HEAD AND NECK: STATE OF THE ART AND PERSPECTIVES

Ph.D. Thesis

Balázs B. Lőrincz, M.D.

**SEMMELWEIS UNIVERSITY
DOCTORAL SCHOOL OF THEORETICAL MEDICAL SCIENCES**



Consultant: György Wéber, MD, PhD

Reviewers: László Tamás, MD, PhD

László Rovó, MD, PhD

Head of the final examination board: Gábor Repássy, MD, PhD

Members of the final examination board: Tamás Haidegger, PhD

Attila Szijártó, MD, PhD

Budapest

2014

TABLE OF CONTENTS

ABBREVIATIONS	5
1. INTRODUCTION	6
1.1. Background	6
1.2. TORS for Oropharyngeal Squamous Cell Carcinoma (OPSCC)	9
1.3. TORS for Hypopharyngeal Squamous Cell Carcinoma (HPSCC)	10
1.4. The Appropriate Neck Dissection for Patients Undergoing TORS	10
1.4.1. Cultural and historical background of neck dissection techniques	12
1.4.2. Timing of Neck Dissection in Patients Undergoing TORS	13
2. OBJECTIVES	15
2.1. Determining the Oncological Value of TORS for HNSCC	15
2.2. Assessing the Functional Value of TORS for HNSCC	15
2.3. Prospectives, Future Directions	15
3. METHODS	16
3.1. Prospective Data Collection	16
3.2. Clinical Pathway	16
3.3. Patients with OPSCC	17
3.3.1. Patient Selection	17
3.3.2. TORS Procedure	18
3.4. Patients with HPSCC	20
3.4.1. Patient Selection	20
3.4.2. TORS Procedure	22
3.5. The Appropriate Neck Dissection	24
3.5.1. Prospective Data Collection of All Neck Dissections	24
3.5.2. Patient Cohort	25
3.5.3. Inclusion Criteria	25
3.5.4. Exclusion Criteria	26
3.5.5. Surgical Oncology Concept	26

3.5.6. Surgical Technique	27
3.5.7. Statistical Methods	28
3.5.8. Management of the Neck in Patients Treated with TORS	29
3.5.9. Timing of Neck Dissections Related to the TORS Procedure	31
3.5.9.1. TORS Procedures	32
3.5.9.2. Neck Dissections	33
3.6. Defining the Standard TORS-Algorithm	34
3.6.1. Constructing the TORS-Management Framework	35
3.6.1.1. Access	36
3.6.1.2. Advantages of TORS over Conventional Modalities	37
3.6.1.2.1. Advantages of Transoral Surgery over CRT	37
3.6.1.2.2. Advantages of TORS over TOLM/Open Surgery	39
3.6.1.3. The Human Papilloma Virus Epidemic and TORS	40
4. RESULTS	43
4.1. Patients with OPSCC	43
4.1.1. Preliminary Oncological Outcomes	43
4.1.2. Functional Outcomes	47
4.2. Patients with HPSCC	49
4.2.1. Preliminary Oncological Outcomes	50
4.2.2. Functional Outcomes	52
4.3. Neck Dissection Outcomes	53
4.3.1. Statistical Analysis	53
4.3.1.1. Harvested Lymph Node Count Comparison per Level	53
4.3.1.2. Overall Nodal Yield	54
4.3.2. Timing of Neck Dissection in Patients undergoing TORS	56
4.3.2.1. Pattern of Spread	56
4.3.2.2. Nodal Yield	56
4.3.2.3. Intraoperative Complications	57
4.3.2.4. Postoperative Complications	57
4.4. Our Concept for TORS	58
4.4.1. Selecting the Ideal TORS Candidate	59

5. DISCUSSION	61
5.1. Discussion of TORS in Oropharyngeal SCC	61
5.2. Discussion of TORS in Hypopharyngeal SCC	63
5.3. Discussion of Neck Dissection for TORS Patients	66
5.3.1. Explaining Level V	66
5.3.2. General Considerations	66
5.4. Discussion of our TORS Concept	68
6. CONCLUSIONS	70
6.1. OPSCC	70
6.2. HPSCC	71
6.3. Neck Dissection	71
6.4. TORS Concept	72
7. SUMMARY	73
8. ÖSSZEFOGLALÁS	74
9. REFERENCES	75
10. PUBLICATIONS	88
10.1. Related to the Ph.D. Thesis	88
10.2. Other Publications	88
11. ACKNOWLEDGEMENTS	90

ABBREVIATIONS

TORS	Transoral Robotic Surgery
TOLM	Transoral Laser Microsurgery
HNSCC	Head and Neck Squamous Cell Carcinoma
OPC, OPSCC	Oropharyngeal Cancer/Squamous Cell Carcinoma
HPSCC	Hypopharyngeal Squamous Cell Carcinoma
SCC	Squamous Cell Carcinoma
HPV	Human Papilloma Virus
CRT	Chemo-Radiation-Therapy
RT	Radiotherapy
PEG	Percutaneous Endoscopic Gastrostomy
QoL	Quality of Life
OS	Overall Survival
DSS	Disease Specific Survival
DFS	Disease Free Survival
IMRT	Intensity Modulated Radiation Therapy
ND	Neck Dissection
SND	Selective Neck Dissection
SSND	Supers elective Neck Dissection
SPECT(-CT)	Single Photon Emission Computed Tomography

1. INTRODUCTION

The multimodality treatment arsenal for head and neck squamous cell carcinoma has been recently supplemented by transoral robotic surgery (TORS) [1]. It is a novel method to decrease treatment-related morbidity while maintaining comparable oncological results to conventional surgery and to primary chemoradiation therapy. TORS has been approved by the United States Food and Drug Administration (FDA) for T1 and T2 malignancies of the upper aerodigestive tract in December 2009. Since then, the transoral application of the daVinci Surgical System (Intuitive Surgical, Inc., Sunnyvale CA, USA) has considerably spread in Europe as well [2].

1.1. Background

TORS has become well established in recent years, and is used mostly for the resection of oropharyngeal as well as of select hypopharyngeal and supraglottic tumours. It is interesting to note that the sudden shift towards first-line TORS in the U.S. has occurred despite preceding decades of declining utilization of surgery in favor of primary chemoradiation therapy (CRT) across the majority of U.S. head and neck cancer centers. The explanation for the rapid acceptance and implementation of first-line TORS therapy in the U.S. is threefold. Most importantly, mounting skepticism – especially among head and neck surgeons – as to the net benefit of first-line CRT in terms of overall survival (OS) and quality of life (QOL) in comparison to first-line definitive surgery for head and neck squamous cell carcinoma (HNSCC) has provided the impetus towards a shift to the latter [3]. In Table 1., we listed the percutaneous endoscopic gastrostomy (PEG)-dependency data of three recent studies [4-6] to compare functional (swallowing) outcomes of primary 3D conformal radiotherapy (RT) with chemotherapy [4], primary intensity modulated radiotherapy (IMRT) with chemotherapy [4], transoral laser microsurgery (TOLM) [5] and TORS [6] for oropharyngeal cancer.

Table 1.

Comparison of primary chemoradiotherapy, transoral laser microsurgery (TOLM) and transoral robotic surgery (TORS) with regards to PEG-dependency

	No. of patients	T1 and T2 proportion	Surgery alone, without adjuvant therapy	PEG-dependency at 1-year post-treatment
Lohia et al. 3D conformal RT+CT	50	50%	n/a	35% (median: 259 days)
Lohia et al. IMRT+CT	95	63%	n/a	13% (median: 154 days)
Grant et al. TOLM	59	66%	53%	8% (median: not reported)
Lorincz et al. TORS	35	97%	37%	0% (median: 26 days)

Abbreviations:

PEG: percutaneous endoscopic gastrostomy

3D conformal RT+CT: three-dimensional conformal radiotherapy with chemotherapy

IMRT+CT: intensity modulated radiotherapy with chemotherapy

TORS: trans oral robotic surgery

TOLM: trans oral laser microsurgery

The sudden change in HNSCC demographics – from older patients with a long history of tobacco and alcohol abuse to younger patients without substance abuse issues – due to the human papillomavirus (HPV)-associated oropharyngeal cancer (OPC) epidemic[7-10] has only served to compound the skepticism surrounding the benefits of first-line CRT use [11]. The long-term effects of primary CRT versus first-line surgery

on QOL and OS must be carefully considered in this new patient demographic, whose life expectancy is decades longer than the traditional HNSCC patient [12, 13].

Second, the widespread use of first-line CRT over the past several decades in the U.S. inevitably led to the graduation of successive cohorts of head and neck surgeons with little experience in performing open procedures for such cancers. Third, the failure of trans-oral laser microsurgery (TOLM) to gain truly widespread popularity in the U.S. provided fertile grounds on which a novel minimally invasive technique could take hold [3].

By contrast, a different situation exists in continental Europe with regards to the preferred first-line treatment for OPC, hypopharyngeal and supraglottic cancer. Although primary CRT plays a significant role in the management of such tumors, first-line surgery has remained a popular option here. TOLM was incorporated into most head and neck training programs, with open resections for such cancers remaining a viable treatment option. This situation has not changed in the face of the HPV-epidemic, which has also struck Europe,[10] with many head and neck surgeons (especially in Germany and France) still favoring surgery in such cases, whether it consists of TOLM, partial laryngeal framework surgery, lateral pharyngotomy or open resection with a lip split or mandible split.

Before the advent of robotic surgery and the HPV epidemic, proponents of first-line CRT for T1-T2 pharyngeal and laryngeal carcinomas in centers where TOLM was not popularized had strong arguments for its use. The operative risk and morbidity associated with an open procedure remains a compelling argument against surgery, especially for the classic HNSCC patient with systemic co-morbidities associated with decades of substance abuse. However, the increasingly younger patient demographic combined with the novel minimally invasive approach offered by TORS is tipping the scale back towards definitive surgery across the U.S. as well.

The low morbidity trans-oral access offered by TORS has not generally been recognized as a completely novel approach in Europe, where TOLM has been widely accepted and used for decades. Despite the introduction of TORS and the accessibility

of the daVinci Surgical System in most academic centers, TOLM remains a gold standard treatment option for first-line management of pharyngeal and laryngeal tumors across many European centers. By comparison, in the U.S. – where oncologic TOLM has not been as widely popular as in continental Europe and reported data has been mainly restricted to some high-volume centers [5, 14, 15] – TORS is now generally considered the preferred trans-oral surgical modality for such tumors. In addition to a quicker learning curve [16], the TORS approach features other important advantages over TOLM that will be discussed. With proper patient selection, the advantages of TORS present strong arguments for its first-line use in place of CRT in the U.S. and in place of TOLM in Europe.

1.2. TORS for Oropharyngeal Squamous Cell Carcinoma (OPSCC)

TORS, as a surgical tool, has some great advantages over conventional open surgery [17] and over the tangentially cutting traditional transoral laser microsurgery, those being low-morbid surgical access (vs. open surgery through a lip split, mandible-split or lateral pharyngotomy) under excellent 3D-HD visualisation and en bloc, multi-planar manual margin control (vs. transoral laser surgery) as the most important TORS-features and selling points [18]. However, most patients eligible for TORS could be potentially treated with primary chemoradiation as well [19], with comparable oncological outcomes.

Unlike most publications on primary chemo-radiotherapy with good results for oropharyngeal cancer, our oropharyngeal TORS-population includes only 34% HPV-positive patients, which may make direct comparisons difficult. The main question here to ask when considering TORS is whether the treatment-related morbidity of TORS, combined with the added morbidity of the potentially still necessary adjuvant therapy, is lower than the morbidity of primary chemoradiation [20][21].

There is Level 2c evidence in the literature [13] showing that early oropharyngeal cancer can be treated with surgery alone with high long-term quality of life. Long-term survivors of oropharyngeal cancer benefit from complete surgical resection, as

surgically treated patients complain significantly less about dry mouth and dental problems, compared to patients treated with primary chemo-radiation. Primary surgery with postoperative radiotherapy in selected patients with limited primary tumours and advanced neck disease renders excellent quality of life [13, 22].

In our study, we summarize and evaluate our initial experiences with oncological TORS procedures, based upon the prospectively collected clinico-pathological data of our first 35 TORS-patients with oropharyngeal cancer.

1.3. TORS for Hypopharyngeal Squamous Cell Carcinoma (HPSCC)

While most published TORS-data focus on the oropharynx and a new paradigm shift is being witnessed regarding the primary treatment of HPV-driven oropharyngeal cancer, there has been much less attention paid to the hypopharyngeal application of TORS so far. Nevertheless, TORS provides with definitive advantages [23, 24] over the tangentially cutting traditional transoral laser microsurgery (TOLM) in the supraglottic region and in the hypopharynx, those being excellent 3D-HD visualisation with a great depth of field and en bloc, multi-planar manual margin control, avoiding piece-meal resections. Its benefits, however, are most obvious when the patient does not need adjuvant therapy. Therefore, appropriate patient selection is of paramount importance [18, 25].

1.4. The Appropriate Neck Dissection for Patients Undergoing TORS

In surgical oncology, there is evidence that the overall number of harvested regional lymph nodes, also known as the *nodal yield* of regional lymphadenectomies, is an independent prognostic factor in colon [26, 27], colorectal [28], bladder [29-31], prostate [32], penile [33], esophageal [34], gastric [35] and breast cancer [36]. This is applicable even to node negative cases, i.e. irrespective of the metastatic involvement of the removed lymph nodes [37].

In head and neck cancer, the same has been shown in papillary thyroid [38, 39], and squamous cell cancer of the oral cavity [37, 40-43], the oropharynx [42] and the hypopharynx [42, 44]. A recent international multicenter analysis of pooled individual patient data confirmed that nodal yield is a robust independent prognostic factor in patients undergoing selective neck dissection (SND) for cN0 oral squamous cell cancer (OSCC) [43].

Further, nodal yield may be a useful parameter for the quality assessment and for the accountability of surgical treatments, where standardisation of surgical technique will be necessary to allow reproducibility and statistical comparison of surgical and non-surgical therapeutic options.

In this study, having accepted the oncological importance of nodal yield described by other authors as listed above, our aim was to show how this independent prognostic factor can be influenced by the applied surgical concept and dissection technique. This is the first paper in the head and neck cancer literature to show a statistically significant nodal yield advantage correlated to a certain surgical technique.

Several factors have an influence on nodal yield. First, individual patient anatomy is variable and the total number of „available“ lymph nodes in a specific patient is unknown [45]. However, cadaver data suggest that there are *at least* a total of 30-40 lymph nodes in Levels I-V on one side of the neck in average [46]. Second, the surgeon should remove as many lymph nodes from the relevant neck levels as possible [47], in order to bring the *harvested lymph node count* as close to the (otherwise unknown) *available lymph node count* as possible. Finally, the thoroughness of the histopathological workup has a significant impact on the *documented lymph node count*, presented by the pathologist [48]. The latter is the only information we may learn and use as the basis of our clinical decision management, while each step is likely to represent a certain data loss.

Although therapeutic decisions (e.g. offering or omitting adjuvant treatment) can only rely on the staging based on the documented lymph node count, the course of the

disease and ultimately the patients' life is affected by the harvested lymph node count. Even if a removed, clinically negative, but in reality micrometastatic node is missed by the pathologist and goes unnoticed [37], that specific involved node has already been removed from the patient, so they are more likely to stay disease free irrespective of the documented, possibly incorrectly pN0-staged neck [37].

1.4.1. Cultural and Historical Background of ND Techniques

What we later in this paper refer to as the *fascia unwrapping* or *horizontal technique*, was first described by Osvaldo Suarez and popularized in the Latin world in the 1960s, based on his concept of the then-so-called functional neck dissection (not to be confused either with the selective or with the modified radical neck dissection, as it will be detailed later in this text).

Suarez published his works in Spanish. As his papers have been translated into English during the 1970s and 1980s, North-American and British surgeons started to teach this technique to a much broader audience in the United States and in the countries of the Commonwealth from the 1990s, thanks to the clinical fellowship-based training system of the English-speaking world.

By the 1990s and 2000s, as a result of this cultural cross-fertilization, the fascia unwrapping or horizontal technique has become the predominant dissection method when doing selective neck dissections in the United States and in the entire Commonwealth. In these countries, this technique today is the state of the art, without even having a specific name: this is the way selective neck dissections are done by default.

In continental Europe, however, selective neck dissections are, conceptually, still mostly seen as further modifications of the modified radical neck dissection, not as an entirely different functional concept, but as further derivatives of the original radical concept of George Crile from 1906. The latter has been typically performed in a vertical, i.e. caudal to cranial or cranial to caudal fashion. Thus, the selective neck

dissection kept this dissection principle in continental Europe, especially among maxillofacial surgeons but also in the case of many otolaryngologists, having only sporadically been influenced by the British-American-Australasian clinical fellowship training programmes.

1.4.2. Timing of Neck Dissection in TORS Patients

Transoral robotic surgery (TORS) for T1 and T2 head and neck squamous cell carcinoma (HNSCC) has become an established primary treatment option in the oropharynx, hypopharynx and supraglottic larynx in Europe [2, 6, 25] and worldwide [1, 18, 23, 49-51]. The surgical treatment of oropharyngeal, hypopharyngeal and laryngeal cancer frequently includes the appropriate regional lymphadenectomy of the neck, also known as neck dissection (ND). However, the ideal timing of neck dissection in TORS-patients remains controversial, where the priority of the assumed oncological advantages of a concurrent procedure is often challenged by obvious time constraints, especially in Europe, where the robot is available for most head and neck departments only in limited time slots weekly or even fortnightly.

Besides the low level evidence in the literature [52-54] regarding the best timing of neck dissection for patients undergoing TORS for their primary disease, there are some common sense considerations about the advantages and disadvantages of concurrent and staged neck dissections in this context.

Performing the neck dissection in the same general anaesthesia as the TORS procedure (concurrent ND) may provide with some benefits. As the definitive treatment for the primary tumour and for the neck lymph nodes can be done in a single session, it is more convenient for the patient, may reduce the overall anaesthetic risk of the procedure, the hospitalization time, and the associated costs as well. Further, the concurrent ND would incur no delay in patient progress towards a possibly necessary adjuvant therapy. Another argument is the option for vessel ligation during the neck dissection to prevent postoperative bleeding from the primary TORS-resection site, upon the surgeon's

preference [1], and the possibility to conveniently include an elective, temporary tracheotomy into the neck incision, should the latter be necessary for airway safety.

In contrast, the staged neck dissection, i.e. a ND performed in a time interval after the primary tumour resection, may have some other advantages. These include a possibly less frequent intraoperative pharyngocervical fistula formation, more convenient theatre list planning – including the distribution of robotic slots among the involved departments –, the opportunity to address close or positive resection margins reported in the final histopathology after TORS, and the possibility to close a tracheotomy if it was done during the TORS-procedure previously. A delayed neck dissection may even prevent an elective tracheotomy during the primary TORS-session, by reducing laryngopharyngeal mucosal swelling due to the untouched outer neck.

This issue is well known to the European TORS-community. Our team, as one of the most experienced TORS-units in Europe with over a hundred robotic cases done in the past 3 years, is frequently being asked about our practice and experiences in this regard. At the beginning, our firm intention was to do all neck dissections on the same day, and we did so with our first 20-25 TORS-patients. With two robotic cases on the same list, some of them requiring bilateral neck dissections, this practice stretched the limits of our scrub nurses and the anaesthesia team, especially at the beginning of our robotic learning curve when patient turnover, patient positioning, docking the robot and robotic console work took much longer time than it does today. For this reason, we changed our practice and started to do the neck dissections in a timely staged fashion. The purpose of the present study was to provide our institutional experience on the safety and efficacy of staged versus concurrent ND, with special regards to intraoperative pharyngocervical fistula rate, postoperative complications and number of harvested lymph nodes.

2. OBJECTIVES

2.1. Oncologic Value of TORS for HNSCC

The goal of this work was to assess the feasibility, resection margins, safety and oncological value of TORS in patients with HNSCC. The main target population is represented by patients with T1 and T2 oropharyngeal, hypopharyngeal and supraglottic cancer, where primary chemoradiation or transoral laser surgery are feasible treatment options as well. The main purpose of transoral robotic surgery in these patients is to maintain oncologic safety while reducing treatment-related morbidity.

2.2. Functional Value of TORS for HNSCC

While maintaining oncological safety comparable to that of primary CRT or TOLM, our purpose was to achieve better postoperative swallowing function compared to primary CRT. Omitting or reducing adjuvant treatment after primary surgery is equally paramount. With better resection margin control, appropriately selected and surgically staged patients may avoid adjuvant treatment or at least reduce adjuvant radiation therapy by 10 Gy and omit the chemotherapy component.

2.3. Perspectives, Future Directions

The above trend is expected to further unfold in terms of keeping the number of treatment modalities at the minimum, without compromising oncologic safety, especially in HPV-driven tumours. In addition to omitting or reducing adjuvant therapy, even surgery alone may become more conservative as well. In the primary tumour sites of the upper aerodigestive tract, real-time mass spectrometry evaluation of the surgical margins from the combustion products of monopolar cautery, coupled with TORS, may avoid unnecessarily large resections. In the outer neck, hot spot guided sentinel level superselective neck dissections (HSG SL-SSND) in appropriately staged patients may reduce the extent of resection to levels II and III using radiotracer injection during the initial panendoscopy and SPECT-CT prior to the neck dissection.

3. METHODS

3.1. Prospective Data Collection

The following set of data was collected in a prospective manner for each patient underwent TORS at our institution: Case number, date of presentation, date of diagnosis, date of procedure, patient age at TORS, patient gender, cTNM-classification, pTNM-classification, overall tumor stage, tumor site, tumor side, p16-status, HPV-DNA-status, smoking pack years, alcohol history, margin status, closest margin, neck dissection levels done, nodal yield of neck dissection, number and level of positive lymph nodes, presence of extracapsular spread (ECS), adjuvant therapy, dosis of radiation in Gray (Gy) if applicable, chemotherapy, post-operative bleeding, need of tracheotomy, days intubated, intensive care unit (ICU) days, intermediate care (IMC) days, nasogastric (NG) tube days, percutaneous endoscopic gastrostomy (PEG) tube days, speech function, swallowing function, duration of follow-up, recurrence, time to recurrence and site of recurrence if applicable, alive or dead, date of death if applicable, alive with or without disease, dead with or without disease, modality of salvage if applicable, among other data concerning the technical details of the robotic procedures, i.e. which Endowrist instruments, which optic, which retractor etc. were applied for each specific procedure.

3.2. Clinical Pathway

For initial presentation, the patients have been referred to the Otolaryngology Outpatient Clinic of our tertiary referral center either by a primary care physician or by a private ENT-specialist in town. After clinical examination, preoperative work-up consisted of a magnetic resonance imaging scan of the head and neck, computed tomography of the thorax and sonography of the abdomen. This was followed by an examination under anaesthesia (EUA), i.e. a panendoscopy with biopsies, resulting in the histological verification and tumor mapping of the disease. The panendoscopy was performed by the same surgeon using the same TORS-specific retractor [55] (Laryngeal Advanced Retractor System (LARS) by Fentex Medical, Neuhausen, Germany and/or

Feyh-Kastenbauer modified by Weinstein-O'Malley (FK-WO) by Olympus-Gyrus ACMI-ENT, Bartlett TN, USA) as in the case of the robotic procedures, to be able to accurately assess accessibility with the robotic system, as an inherent part of the patient selection.

Having all these results within two weeks after initial presentation, the patients were finally discussed in detail at the Multidisciplinary Head and Neck Tumor Board of our Comprehensive Cancer Centre, critically considering TORS among other adequate treatment options before having decided specifically for this modality. After having completed surgical treatment, results of the final histology were discussed again at the Tumor Board regarding adjuvant therapy [56][57][58]. After completion of therapy, all patients have had a three-monthly follow-up schedule.

3.3. Patients with OPSCC

3.3.1. Patient Selection

Following the above pathway, thirty-five patients with appropriately staged oropharyngeal cancer were selected for our initial robotic surgery series (Table 2). They underwent TORS between September 2011 and April 2013 (19 months' timeframe) as the primary treatment modality along with an appropriate uni- or bilateral neck dissection, as indicated, providing the largest single-institution TORS-cohort to date in the German-speaking countries.

These thirty-five patients with oropharyngeal cancer had the following T-classifications: Nineteen patients presented with a T1-disease and sixteen patients had T2-tumors, while the overall staging represented TNM stage I-II in 13 cases and TNM stage III-IV in 22 cases. Our thirty-five patients with oropharyngeal primaries [59][51] included the following subsites: the base of tongue (n=14) [60], the tonsillo-lingual angle (n=5), the tonsil (n=13) [50] and the soft palate (n=3).

Table 2.

Patient characteristics of our oropharyngeal TORS patients[6]

Variables	No. of patients (%)
Age, y, median 65 y, range 49–84 y	
<65	17 (48.6)
≥65	18 (51.4)
Sex	
Male	26 (74.3)
Female	9 (25.7)
Tumor site	
Oropharynx	
Base of tongue	14 (40)
Tonsil/lingual	5 (14.3)
Tonsil	13 (37.1)
Soft palate	3 (8.6)
pT classification	
T1	19 (54.3)
T2	15 (42.9)
T3–T4	1 (2.8, upstaged from cT2)
pN classification	
N0	13 (37.1)
N1	8 (22.9)
N2	13 (37.1)
N3	1 (2.9)
TNM stage	
I–II	13 (37.1)
III–IV	22 (62.9)
HPV-drivenness	
p16-positive	18 (51.4)
HPV-DNA-positive	12 (34.3)
HPV-positive	12 (34.3)
HPV-driven	9 (25.7)

Abbreviation: HPV, human papillomavirus

3.3.2. TORS Procedure

After obtaining informed consent, all TORS-procedures and neck dissections have been performed under general anaesthesia with a transoral intubation using a reinforced, metal-coated laser-tube both cuffs blocked with air, only to provide protection from the proximity of the monopolar dissection. The surgeries were performed consistently by

the same TORS-team, licensed according to the official daVinci-TORS-training pathway approved by Intuitive Surgical, Inc. [16].

Our team consists of a fellowship-trained consultant head and neck surgeon as the console surgeon (first author), specialist registrars as surgical assistants (second and third authors) and TORS-licensed scrub nurses, coordinated by a multidisciplinary expert head and neck oncologist, also trained in and licensed for transoral robotic surgery (senior author). Consistency in the anesthesia team has also been encouraged but not always achieved due to scheduling issues [61].

All patients have been operated using the following surgical equipment: Soft Spandex lip and buccal retractor (Ortho-Care, Saltaire, West Yorkshire, UK); exposure obtained either using the LARS- [55] or the FK-WO-retractor system (trade names described previously); daVinci Si Surgical System being docked from the right side of the patient approximately in a 30°-angle between the patient cart and the operation table, as well as 5mm and 8mm-Endowrist instruments (Intuitive Surgical, Inc., Sunnyvale CA, USA).

The Endowrist-instruments included 8mm and 5mm monopolar permanent cautery spatula, 8mm Maryland bipolar forceps, 5mm Maryland dissector, 8mm fenestrated bipolar forceps and 8mm monopolar scissors. For oropharyngeal resections, we preferred the combination of a 5mm monopolar spatula with a 8mm Maryland bipolar forceps in the tonsillar and tonsillo-lingual regions, because of the bipolar capability of the latter, and that of a 5mm monopolar spatula with a 8mm fenestrated bipolar forceps in the base of tongue, because of the better grip and traction provided by the latter, an important feature when using monopolar cautery as the power instrument for cutting. A 12mm stereo endoscopic camera was used in each case: a 0°-optic for tonsillar and soft palate resections, and a 30°-optic (looking upwards) for most base of tongue resections.

All of our TORS-resections were performed using monopolar dissection. The power generator was used exclusively in coagulation mode (blue), also when cutting, as this waveform provides a lot less traumatic dissection, less collateral conducted heat, less bleeding as well as the resection margins can be more accurately assessed by the

pathologists. These observations are supported by our non-robotic surgical practice and by other expert head and neck surgeons as well. The electrocautery power settings ranged between 10 and 25 Watts, usually being set on 15-20W for bipolar and on 20-25W for monopolar cautery. It is paramount to avoid higher energy settings when operating in the regions of the head and neck in order to avoid oedema and to reduce the risk of nerve injuries and postoperative bleeding [62]. If the effectivity of the dissection is insufficient, it is usually a matter of too little tissue traction rather than too low power settings. If this occurs, appropriate traction must be provided in first place, instead of increasing the power of the electrocautery.

In order to avoid postoperative mucosal oedema and swelling, all TORS procedures are performed in a slightly tilted head up position, so that the head is at the highest point of the patient's body even with the neck extended. In addition to this, an i.v. single shot of 250mg methyl-prednisolon is given twice intraoperatively: at the beginning of the robotic resection for the first time, and once again after having completed the resection. Following the procedure, a nasogastric tube is placed while the patient is still sleeping. Patients were kept intubated for one night at the intensive care unit (ICU) after TORS, to keep their blood pressure low in order to reduce the risk of postoperative bleeding and to let the steroids work to reduce postoperative oedema before extubation to prevent airway obstruction [63]. Extubation took place the following morning in the presence of the surgeon. With this standard procedure, we managed to reserve elective tracheotomy for very selected cases (3 out of 35 patients, 8.6%), whose estimated risk of airway issues and postoperative bleeding was significantly higher than usual.

3.4. Patients with HPSCC

3.4.1. Patient Selection

Since September 2011, we have been conducting a prospective TORS-trial at our institution, which initial part included 50 patients with T1 and T2 malignancies of the upper aerodigestive tract [6]. Among them, five patients underwent TORS and concurrent selective neck dissection for early hypopharyngeal cancer. In the present

subset analysis, we summarize and evaluate their clinico-pathological data in order to determine whether TORS is a suitable first-line treatment for early hypopharyngeal squamous cell carcinoma.

After initial presentation, clinical examination and appropriate radiological staging, a panendoscopy was performed in each case by the same surgeon using the same TORS-specific retractor [55] (Laryngeal Advanced Retractor System (LARS) by Fentex Medical, Neuhausen, Germany and/or Feyh-Kastenbauer modified by Weinstein-O'Malley (FK-WO) by Olympus-Gyrus ACMI-ENT, Bartlett TN, USA) as in the case of the robotic procedures, to be able to accurately assess accessibility with the robotic system [63], as an integral part of the patient selection. In the present subgroup of patients, three tumours were restricted to the lateral wall and apex of the piriform sinus, while the medial wall of the piriform sinus and consequently the aryepiglottic fold was also infiltrated in two further cases. The patients' demographic data and tumour characteristics are listed in Table 3.

Table 3.
Patient characteristics of our hypopharyngeal TORS patients[25]

Patient no.	#1	#2	#3	#4	#5
Age (years) median 64 years	64	62	57	64	70
Sex	Male	Male	Male	Female	Male
cTNM (C2)	cT2 cN0	cT1 cN2b	cT2 cN0	rcT1 cN0	cT1 cN0
pTNM (C4)	pT2 pN0	pT2 pN2b	pT2 pN0	rpT1 pN0	pT1 pN0
Stage	II	IVA	II	I	I
Tumour site	PF/AEF	PF	PF/AEF	PF	PF
p16/HPV-DNA	Pos./neg.	Neg./neg.	Neg./neg.	Neg./neg.	Pos./pos.
Alcohol	Abuse	Abuse	Abuse	No	No
Nicotine p/y	40	<10	20	<10	No
HPV-driven	No	No	No	No	Yes

Abbreviations:

PF: piriform fossa

AEF: aryepiglottic fold

HPV: human papilloma virus

p/y: pack years

3.4.2. TORS Procedure

After obtaining informed consent, all TORS-procedures and neck dissections have been performed under general anaesthesia with a transoral intubation using a reinforced, metal-coated laser-tube both cuffs blocked with air, only to provide protection from the proximity of the monopolar dissection [61]. The surgeries were performed consistently by the same TORS-team [16], licensed according to the official daVinci-TORS-training pathway approved by Intuitive Surgical, Inc. Consistency in the anesthesia team has also been encouraged but not always achieved due to scheduling issues [61].

In each hypopharyngeal TORS-procedure, the Endowrist instrumentation consisted of a 5mm monopolar permanent cautery spatula and a 5mm Maryland dissector. These 5mm instruments allow a significantly higher degree of freedom than the 8mm instruments do, which is especially beneficial in the hypopharyngeal and supraglottic resections in our experience. A 12mm stereo endoscopic camera was used in each case with its 30°-optic looking upwards. The monopolar power generator was used in coagulation mode (blue), set as low as at 15 Watts, in order to avoid excessive conducted heat and oedema, as well as to allow accurate histological margin assessment. Surgical technique and outcomes are summarized in Table 4.

Table 4.: Surgical outcomes of our hypopharyngeal TORS patients[25]

Patient no.	#1	#2	#3	#4	#5
Closest margin	4 mm	5 mm	5 mm	5 mm	6 mm
Surgical technique	Monopolar dissection	Monopolar dissection	Monopolar dissection	Monopolar dissection	Monopolar dissection
Endowrist instruments	5 mm monopolar and 5 mm Maryland	5 mm monopolar and 5 mm Maryland	5 mm monopolar and 5 mm Maryland	5 mm monopolar and 5 mm Maryland	5 mm monopolar and 5 mm Maryland
Postop oedema	No	No	Yes	No	No
ICU/IMC days	2/0	5/3	1/1	1/0	1/0
Tracheotomy	No	No	Elective	No	No
NG-tube, days	3	18	7	0 (PEG)	4
PEG-tube	No	Yes, on day 18 postop.	No	Preop.	No

Abbreviations:

ICU: intensive care unit

IMC: intermediate care

NG: nasogastric tube

PEG: percutaneous endoscopic gastrostomy

As the access to the tumour is of utmost importance, selection of the retractor blade must be individual and appropriate. Currently, there are two major retractor systems on the market, specifically designed for TORS: the Laryngeal Advanced Retractor System (LARS) by Fentex Medical [55], and the Feyh-Kastenbauer modified by Weinstein-O'Malley (FK-WO) by Olympus-Gyrus. The most commonly used blades of both systems are shown on Fig.1. When performing TORS in the hypopharynx, the working space is much more confined than it is in the oropharynx [64]. Therefore, proper selection of the blade has an even greater impact on the access. On Fig.1., the longest blades provide with the best access to the piriform fossa, specifically the ones marked here as FK-WO 5 and LARS 1 and 2. Other ones marked as FK-WO 1-4 and LARS 3-4 are designed for the base of tongue.



Fig.1: Several blades of the FK-WO and LARS retractor systems[25]photo by BBL

From left to right: FK-WO 1, 2, 3 and 4 for the base of tongue, FK-WO 5 for the piriform fossa, LARS 1 and 2 for the piriform fossa, LARS 3 and 4 for the base of tongue. The longest and narrowest blades are best suitable for hypopharyngeal exposure.

3.5. The Appropriate Neck Dissection

This is a single-institution, prospective study with internal control group (Level of evidence: 2A). Our primary objective was maximizing the nodal yield at the lowest possible morbidity. In practice, this translates into preserving all anatomical structures other than lympho-fatty tissue. On one hand, no structure is supposed to be sacrificed on the account of a higher nodal yield; on the other, preserving important structures should not compromise nodal yield [65].

To balance these two goals, we found that the original functional concept of Osvaldo Suárez, recently popularized by Javier Gavilan in his 2002 book „Functional and Selective Neck Dissection“ [66], is best suitable to fulfil both requirements simultaneously. It can be logically translated into basic surgical principles in a stepwise, standardised fashion, focusing on the functional anatomical dissection along the fascial planes as the oncological barriers in the neck. It is not difficult to learn, easy to standardise and it can be safely reproduced by any head and neck surgeon, if the concept is well understood [67].

3.5.1. Prospective Data Collection of All Neck Dissections

In this spirit, we gradually implemented the fascia unwrapping technique at our department, prospectively collecting clinico-pathological data of our neck dissection patients from February 2011. Until March 2013 (26 months), a total of 150 eligible patients were included in this comparison, operated by the same surgical team, having undergone a total of 223 neck dissections (including 73 bilateral procedures). The patients were divided into two groups, non-randomised, in a stepwise fashion according to the learning curve of the team, in order to compare these two surgical techniques and their possible effect on nodal yield.

3.5.2. Patient Cohort

Eighty-two patients underwent neck dissection with the standardised fascia unwrapping technique (Group 1, horizontal, subfascial dissection with „fascia unwrapping“), while 68 patients were operated without specifically appreciating the fascial planes of the neck, dissecting in a caudal to cranial fashion (Group 2, vertical dissection), all performed by the same surgical team. The specimens were removed en bloc in both groups. Before handing them over to the pathology [68], they were divided into individual levels by the surgeon, allowing the pathologist to identify the level of origin for each part of the specimen.

Neck dissection specimens were processed and evaluated likewise consistently by the same pathologists in a predetermined, standardised manner. The pathologists were not aware of which dissection technique was used in which case. Clinical and pathological staging, type of neck dissection, the extent of neck dissection in terms of neck levels included, gender, laterality, technique of neck dissection, total number of lymph nodes harvested, lymph node count per each level and lymph node ratio were recorded.

3.5.3. Inclusion Criteria

All neck dissections containing at least 3 levels in any given combination were included, both N0 and N+, as long as the latter did not show evidence of extracapsular spread (ECS), so that the fascial planes still could be respected. Distribution of N0 and N+ necks were equal in the two groups. Types of neck dissection included Levels I-III, Levels I-IV, Levels I-V, Levels II-IV and Levels II-V, according to their primary tumour sites. Primary sites included T1 and T2 oral cavity (Levels I-III, I-IV or comprehensive), T1 and T2 oropharynx (Levels II-IV, I-IV or comprehensive), T1, T2 and T3 hypopharynx and larynx (Levels II-IV or comprehensive) squamous cell cancers.

3.5.4. Exclusion Criteria

Patients with clinically or radiologically suspect extracapsular spread (ECS) were not included in this study, as they would not have been eligible for the fascia unwrapping technique. Patients with previous neck surgery and previous radiation therapy to the neck [65], including indications for salvage surgery, were also excluded.

3.5.5. Surgical Oncology Concept

The original functional concept of Osvaldo Suárez is best approached by understanding the fascial compartmentalization of the neck and its role as an oncological barrier [69]. The lympho-fatty system of the neck is contained within a fascial envelope, which may be removed (i.e. unwrapped) with its entire content without taking out other neck structures, allowing maximum nodal yield and minimum morbidity simultaneously.

The surgical technique that made this possible, was initially referred to as *functional neck dissection* because it allowed a functional approach to the neck in head and neck cancer patients, in terms of the *oncological function of the fascial planes*. This is not to be confused with the function of the structures to preserve, such as the internal jugular vein, the spinal accessory nerve and the sternocleidomastoid muscle. The term *functional* refers solely to the *oncological barrier function* of the cervical fascia, and *functional neck dissection* is neither synonymous with the term selective neck dissection nor with modified radical neck dissection, in any regard [70].

Functional neck dissection represents a surgical concept with no implications regarding the extent of the surgery, i.e. the number of levels removed. It still can be either selective or comprehensive, i.e. *functional and selective* or *functional and comprehensive* neck dissection, in terms of what levels are removed. It also can be either elective or therapeutic, depending on the cN-classification from an indication point of view, e.g. an *electively performed functional and selective* neck dissection, or a *therapeutically performed functional and comprehensive* neck dissection.

3.5.6. Surgical Technique

The quantitative goal of maximizing the nodal yield is to be achieved by means of the qualitative concept of functional neck dissection, let it be selective or comprehensive, elective or therapeutic in the same time. *It is not about trying to spot just another couple of more lymph nodes*: it is about elegantly and effortlessly removing *all lymph nodes of the relevant fascial compartments en bloc*, with no structural compromises. The principle is a qualitative approach, which turns out to be quantitatively rewarding, not as its goal, but as its natural and inherent consequence [71].

The surgical technique that derives from the concept of functional neck dissection, is what the authors call as the *fascia unwrapping technique*, in order to avoid further confusion around the widespread misinterpretation of the term functional neck dissection. Fascia unwrapping, and the entire neck dissection incorporating this technique, is typically performed horizontally, from lateral to medial on a broad front (Fig.2.), by dissecting all lympho-fatty tissue in the fascial envelope en bloc, under appropriate tissue traction (Fig.3.), until the anterior front of the internal jugular vein is reached between the posterior belly of the digastric muscle (*cranial border*) and the clavicle (*caudal border*). If this is done properly, the unwrapped fascia envelope will contain all relevantly located lymph nodes (Fig.4.).

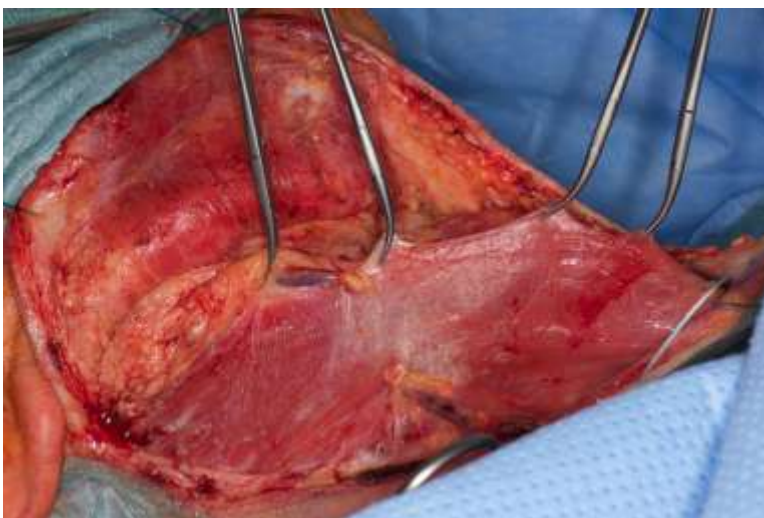


Fig.2: Dissecting the cervical fascia off the leading edge of the sternomastoid muscle horizontally, from lateral to medial on a broad front;photo by BBL

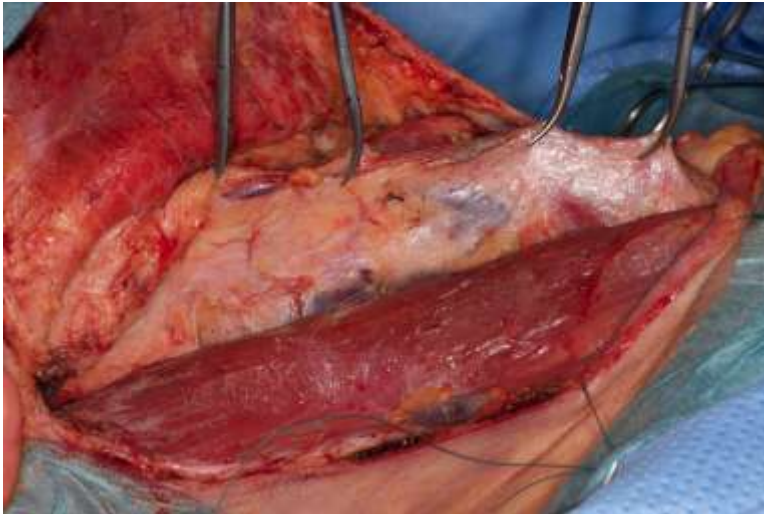


Fig.3: Unwrapping the cervical fascia and its lympho-fatty contents; photo by BBL

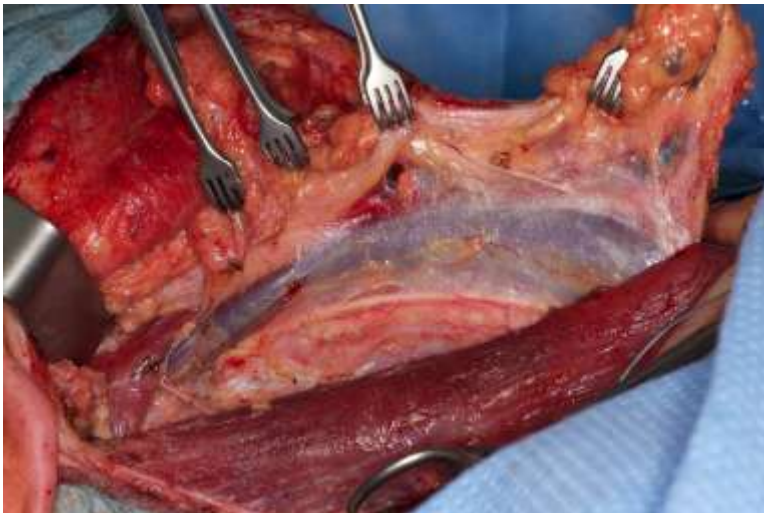


Fig.4: Completion of unwrapping the fascia along the course of the internal jugular vein i.e. the carotid sheath;photo by BBL

3.5.7. Statistical Methods

A multilevel mixed-effects negative binomial regression model was used to compare the number of detected lymph nodes with either surgical technique. To adjust for the cluster structure of the patient, resulting from the different levels within both sides of one patient, the patient as such was included as a random effect. Surgical method, level, side, gender and type of neck dissection were considered as independent variables.

Moreover, all two-way-interactions and the three-way interaction of method, level and side were included and kept in the model if significant (backwards elimination procedure using likelihood ratio test). Adjusted means with 95% confidence interval (CI) are presented. All models present available case analyses. A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using STATA 13 (StataCorp. 2013).

3.5.8. Management of the Neck in TORS Patients

The majority of TORS candidates require either a staging (cN0) or therapeutic (cN+) neck dissection based on the high incidence of nodal spread of pharyngeal and supraglottic HNSCC. Important considerations in the management of the neck in TORS include the extent of neck dissection, the timing of the procedure, nodal yield and the need for post-operative adjuvant therapy. For the cN0 neck, a staging (elective) selective neck dissection (SND) should be performed. Based on work by O'Brien et al, a SND of levels I-IV is also an option for therapeutic management of cN1 disease of the oropharynx and oral cavity.[72]

The timing of the neck dissection is also of significant importance. One of the crucial advantages of TORS over open procedures is the significantly decreased risk of pharyngocutaneous fistula. Following TORS resection of larger T2 tumors, such advantage may be lost if concurrent neck dissection is performed resulting in communication with the pharynx. Furthermore, neck dissection adds considerable amount of surgical time the TORS procedure; in centers that have time-limited access to the daVinci Surgical System, this may prove problematic. For these reasons, we elect in most cases to perform a staged neck dissection 7-10 days following TORS resection of the primary.

The decision regarding the need for adjuvant radiotherapy following neck dissection is dependent on the number of pathologically involved nodes. In the absence of ECE, adjuvant radiation may be avoided for pN0 and pN1 disease. For this reason, the concept of minimum required nodal yield in staging and therapeutic SND for cN0 and

cN1 disease, respectively, is of significant importance. The SND must harvest a sufficient number of lymph nodes in order to statistically represent the neck. To illustrate, omitting adjuvant therapy for a pN0 neck based on the identification of 20 nodes in the pathologic specimen (0/20) is safer than doing so based on a pN0 where only 10 nodes (0/10) were removed.

Discretion must be used whenever TORS is considered as first-line therapy in the presence of cN2 or cN3 disease. The benefit of first-line TORS in decreasing patient morbidity in comparison to primary CRT is not as much present when post-operative adjuvant therapy cannot be significantly reduced. In the absence of ECE, most experts would advocate for 56-60 Gy of adjuvant RT without chemotherapy. In this instance, TORS is justified based on the avoidance of chemotherapy and a reduction in required RT by at least 10 Gy. In the presence of ECE and/or other adverse features, however, most experts advocate for 66 Gy of adjuvant RT with concurrent chemotherapy. Justification for the first-line use of TORS over CRT in these instances is therefore limited, unless future randomized trials demonstrate a survival advantage.

Predicting ECE based on physical examination and imaging is often not straightforward [73]; however, there is an association between increasing nodal involvement and risk of ECE [74]. This is of special significance when considering TORS for HPV-driven tumors, where a small primary is often accompanied by disproportionately advanced nodal disease, which often demonstrates ECE. Although current treatment protocols do not take HPV into account, it is possible that ongoing de-escalation trials may result in reduced adjuvant therapy recommendations for HPV nodal disease with ECE in the future. In the present setting, another option is to use what current intensity-modulated radiotherapy (IMRT) techniques already allow [75] to “de-couple” the primary site and the neck, avoiding significant doses of RT to the central axis and pharyngeal constrictors after a T1/T2 primary is fully resected, while the neck is still treated maximally with CRT. These would serve to justify the use of first-line surgical modalities in HPV-driven tumors even with advanced neck disease.

3.5.9. Timing of ND Related to the TORS Procedure

In this comparison, a total of 41 patients were included with TORS as their primary treatment for HNSCC. Twenty-one patients were defined as the control group, consisting of those treated with a concurrent ND during the same session with TORS. The experimental group included 20 patients undergoing a timely staged ND with a median time interval of 8.40 days (range, 3-28 days) following their TORS procedure. The patients' demographic characteristics, distribution of their primary tumour sites and the pathological TNM staging in the control group as well as in the experimental group are detailed in Table 5.

Data have been collected in a prospective manner from November 2011 to April 2013 at the Department of Otorhinolaryngology, Head & Neck Surgery and Oncology of the University Medical Center Hamburg-Eppendorf, Hamburg, Germany. The purpose of the data collection was to identify the incidence of pharyngocervical communication during the operative procedure as well as that of the postoperative pharyngocutaneous fistula formation, bleeding from the primary resection site and from the neck dissection site, neck hematoma, seroma and infection. Surgical outcome measures included the nodal yield per neck side and also the harvested nodal count broken down into neck levels, with special regards to level Ib and IIa, being the regions of possible fistula formation.

Table 5: Patient characteristics to comparison the timing of neck dissection vs. TORS

Variable	Control group	Experimental group
	No. of patients (%)	No. of patients (%)
Cohort	21	20
Sex		
male	16 (76.2)	15 (75.0)
female	5 (23.8)	5 (25.0)
Age, years	(median 63.9, range 52-81)	(median 66.9, range 47-83)
<65	11 (52.4)	8 (40.0)
≥65	10 (47.6)	12 (60.0)

Tumor site

Oropharynx	19 (90.5)	14 (70.0)
Base of tongue	6 (28.6)	5 (25.0)
Tonsillo-lingual angle	4 (19.0)	2 (10.0)
Tonsil	8 (38.1)	5 (25.0)
Soft palate	1 (4.8)	2 (10.0)
Hypopharynx	2 (9.5)	6 (30.0)
Piriform fossa	2 (9.5)	6 (30.0)

pT classification

T1	9 (42.9)	7 (35.0)
T2	12 (57.1)	9 (45.0)
T3	0	4 (20.0)

pN classification

N0	9 (42.9)	5 (25.0)
N1	5 (23.8)	7 (35.0)
N2a	1 (4.8)	0
N2b	4 (19.0)	6 (30.0)
N2c	0	2 (10.0)
N3	2 (9.5)	0

TNM Stage

I-II	8 (38.1)	4 (20.0)
III-IV	13 (61.9)	16 (80.0)

3.5.9.1. TORS Procedures

After obtaining informed consent, all patients underwent transoral robotic-assisted resection for their oropharyngeal or hypopharyngeal primary tumour using the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA), as described previously by Lörincz et al. [6, 25]. The lateral superior or medial pharyngeal constrictor muscles were partially resected with the tumour en bloc, when oncologically required. The clear margin status of each TORS-resection was confirmed by means of intraoperative frozen section histology; in cases with close or involved margins, an immediate re-resection was performed subsequently, during the same robotic session. A soft silicone nasogastric feeding tube was placed at the end of each TORS-procedure, still in general anaesthesia.

3.5.9.2. Neck Dissections

Appropriate neck dissections were performed according to the clinical and radiological staging of the neck. Even in the cN0-cases, at least an elective, ipsilateral selective neck dissection in levels II-IV was performed. If clinically suspect or positive nodes were detected in extra levels or contralaterally, additional levels or bilateral necks were dissected, respectively. Resection of the submandibular gland was included according to the surgeon's preference upon the presence of clinically suspect lymph nodes in level Ib. Neck dissections were performed either concurrently with the TORS-procedure (control group) or in a staged manner (experimental group).

In the control group, 9 (42.9%) patients received an ipsilateral neck dissection immediately after their primary tumour resection, during the same general anaesthesia session. Twelve (57.1%) patients were concurrently neck dissected bilaterally (Table 6). Patients in the experimental group underwent 10 (50%) ipsilateral neck dissections and 10 (50%) bilateral neck dissections as staged procedures, with the primary tumour resection (first procedure) and the neck dissection (second procedure) in two separate general anaesthesia sessions (Table 6). The median time interval between the two procedures was 8.40 days with a range from 3 to 28 days.

Preoperatively, following physical examination of the neck and a panendoscopy in general anaesthesia, all cervical lymph node levels were examined by means of MRI- and/or CT-scan with contrast, with regards to clinical and radiological evidence of lymph node metastases. In the control group, 14 patients (66.7%) were staged as cN-positive, versus 15 similarly classified patients (75%) in the experimental group. Concerning the levels included in the ipsilateral neck dissections, all patients in both groups underwent a regional lymphadenectomy at least in levels II, III and IV. In addition to these levels, level I was also included in the ipsilateral neck dissection in 18 cases (85.7%) of the control group, whereof 4 patients (19%) also underwent a submandibulectomy as part of the level Ib clearance. In the experimental group, 10 (50%) patients received an ipsilateral level I dissection, with 1 (5%) patient including a submandibulectomy.

Table 6: Patient characteristics to compare the timing of neck dissection vs. TORS

Variable	Control group No. of patients (%)	Experimental group No. of patients (%)
Cohort	21	20
Total ND performed	33	30
unilateral	9 (42.9)	10 (50.0)
bilateral	12 (57.1)	10 (50.0)
Days between TORS and ND	(median 0, range 0)	(median 8.4, range 3-28)
Ipsilateral ND		
Level I	18 (85.7)	10 (50.0)
incl. submandibular gland	4 (19.0)	1 (5.0)
Level II	21 (100.0)	20 (100.0)
Level III	21 (100.0)	20 (100.0)
Level IV	21 (100.0)	20 (100.0)
all other levels	5 (23.8)	3 (15.0)
cN+	14 (66.7)	15 (75.0)
pN+	12 (57.1)	15 (75.0)
pN+ in Level I	0	1 (5.0)
pN+ in Level II	12 (57.1)	11 (55.0)

Abbreviations:

ND = neck dissection,

TORS = transoral robotic surgery

3.6. Defining the Standard TORS-Algorithm

Our standardized approach to include TORS, and to optimize its role in the multidisciplinary management of head and neck cancer patients, are based on the following institutional experience and data:

To date, more than a hundred head and neck cancer patients have been treated using TORS as the primary modality at our department. Of them, the functional and early oncologic outcomes of our first 35 oropharyngeal TORS-patients with one year follow-up have been previously published [6]. Since then, even the 2-year survival outcomes of our first 50 TORS-patients with HNSCC have become available.

The latter, to date unpublished data show their disease specific survival rate at 96%, while the overall survival was 94%. The two-year disease free survival rate was 88%, and the two-year recurrence-free survival was 80%. Of the 10 patients with recurrent disease, local recurrence, nodal recurrence and distant metastasis occurred in five, three, and in two cases, respectively. This results in a local recurrence rate of 10% after 2 years.

From our first 50 consecutive HNSCC TORS-cases, including 43 oropharyngeal, 4 hypopharyngeal, 2 combined hypopharyngeal/supraglottic and 1 supraglottic SCC, twenty-four patients had T1, twenty-three T2, two T3 and one had a T4a primary tumour. There were 18 patients with overall Stage I-II and 32 patients with Stage III-IV disease.

Following transoral robotic resection of their primaries and appropriate neck dissection(s) as indicated, adjuvant treatment could be spared in 20 patients (40%). Another 5 patients refused the recommended adjuvant therapy (two of them later developed recurrent nodal disease, both were successfully salvaged with chemoradiotherapy). Seventeen patients received 60 Gy adjuvant radiotherapy and 8 patients underwent 66 Gy adjuvant chemo-radiotherapy.

In 37 patients (74%) altogether, adjuvant treatment could be either completely spared, or the chemotherapy component could be omitted and the radiotherapy could be reduced by at least 10 Gy, compared to the standard primary chemoradiation protocol with 70 Gy. Adding the 3 patients who refused adjuvant treatment and did not develop a recurrence to date, this figure goes up to 80%.

3.6.1. Constructing the TORS-Management Framework

In constructing a framework for the use of TORS in the multidisciplinary management of pharyngeal and laryngeal malignancies, one must first define the principal management question: What first-line treatment modality is most likely to minimize morbidity and maximize post-treatment function while maintaining oncologic safety?

[3] In considering TORS as the answer, one must be aware that the current surgical access afforded by TORS limits its use primarily to T1-T2 tumors. Some TORS surgeons also advocate for the inclusion of selected T3 tumors as an off-label use of the daVinci Surgical System. Next, one must consider the contemporary geographical first-line modality that TORS would be superseding; in the U.S. it is primarily CRT, whereas in Europe it is TOLM or CRT. As such, the specific advantages and limitations of TORS with respect to the established first-line modality within a given HNSCC center must be clearly defined and communicated to the patient and multidisciplinary treatment team. Third, it is imperative that the treatment team have a clear construct of the current significance of HPV positivity in tumor response to treatment and the impact – or rather, the lack of impact – this should have on the decision to pursue TORS as a first-line modality. Finally, in any discussion of HNSCC, consideration must always be given to proper management of the regional nodal basin in the neck.

3.6.1.1. Access

For TORS to be considered in the treatment algorithm of HNSCC, appropriate access to the tumor must be feasible. Appropriate access is that which is likely to allow for en-bloc resection of the primary with preferably at least 5 mm margins in all planes. In considering TORS over other modalities, the resection must be realistically achievable without the likelihood of significant long-term functional impairment. Appropriate access requires a) the ability to visualize the entire tumor with the daVinci Surgical System endoscope b) the ability to circumferentially access and resect the tumor with the appropriate robotic instruments c) the ability to visualize nearby critical structures and maintain hemostasis.

Prior to multidisciplinary tumor board discussion, the TORS surgeon must be able to reliably assess the feasibility of achieving appropriate access based on physical examination, endoscopy, and imaging. It is critically important to consider patient factors such as mouth opening, dentition, neck length, and jaw size in addition to tumor size and position. At our institution, pre-treatment examination under anaesthesia (EUA) and panendoscopy is done for all potential TORS candidates using the same

mouth gag (retractor system) that will be used during the ensuing robotic procedure, to fit the individual patient's anatomy and tumor and to ensure adequate access will be possible.

3.6.1.2. Advantages of First-Line TORS over Conventional Modalities

In the U.S., the decision to pursue TORS as first-line therapy for T1-T2 oropharyngeal and laryngeal cancers must be made with regards to the expected functional and long-term morbidity advantages TORS provides over conventional CRT. In Europe, the decision to use TORS must be made with respect to CRT from a functional perspective, and with regards to TOLM from technical, economic, and oncologic safety perspectives. As a result, for TORS to be successfully implemented on both sides of the Atlantic, its use must result in less morbidity and better functionality than primary CRT, while providing the surgeon with an economically feasible tool that expands the scope of tumors that may be resected through a minimally invasive trans-oral approach considerably further than what is possible using TOLM.

3.6.1.2.1. Advantages of Minimally Invasive Transoral Surgery over Primary Chemo-Radiation Therapy

First-line CRT with curative intent for HNSCC typically consists of fractionated RT delivered concurrently with chemotherapeutic agents. The most common protocol involves a total dose of 70 Gy delivered using 35 fractions over 7 weeks to the gross tumor volume (GTV), which includes the primary tumor and grossly involved nodes, and a dose of 56 - 60 Gy to the clinically negative nodal basin, known as the clinical treatment volume (CTV). Concurrent weekly delivery with single agent cisplatin or carboplatin is typical, with some favoring the addition of 5-fluorouracil in combination. Single-agent cetuximab is advocated for use in patients with contraindications to the highly toxic platinum agents.

Proponents of first-line CRT often cite the 'organ-sparing' success rates shown in the RTOG 91-11 for laryngeal malignancies.[76] Such 'organ-sparing' advantages over

first-line surgery are increasingly being called into question. Numerous studies have reported long-term PEG-dependency rates on the order of 30-50% following primary CRT for pharyngeal and laryngeal malignancies.[77] This is principally the result of CRT induced fibrotic changes in the base of tongue and pharyngeal musculature leading to severely compromised swallowing function and subsequent aspiration. Other long-term complications of high dose RT to the head and neck – that only tend to worsen over time – include loss of laryngeal sensation, accelerated tooth decay, xerostomia, accelerated carotid stenosis, osteoradionecrosis of the mandible (especially over 60Gy to the tonsillar region), radiation induced sarcomas, and carotid blowouts. These severe complications are routinely seen by head and neck surgeons. It is clear that ‘organ-sparing’ and ‘function-preserving’ are not synonymous; all those involved in the treatment decision process – most importantly the patient – must understand this critical point. Additionally, one must also consider the long-term deleterious systemic effects and impact on overall survival associated with the use of highly cytotoxic chemotherapeutic agents in primary CRT.

Trans-oral surgical approaches to T1 and T2 pharyngeal and laryngeal tumors principally involve tumor excision without defect reconstruction. Such ablative procedures and the resultant post-operative scarring may also result in significantly compromised speech and swallowing function, the latter resulting in PEG dependency. However, such an outcome is exceedingly rare following trans-oral excisions of T1 and most T2 malignancies.[22, 78-80] Larger T2 carcinomas represent a group where the likely oncologic and functional outcomes of a given first-line management plan – be it CRT, open surgery with or without free-flap reconstruction, or trans-oral approaches – must be carefully considered. Although controversial, most experts would currently agree that open surgery with free flap reconstruction for T3 and T4 carcinomas of the upper aerodigestive tract is unlikely to deliver significantly superior functional results in terms of deglutition and articulation over primary CRT.

The ideal first-line surgical candidate is one with disease that is completely amenable to resection without the need for adjuvant therapy. Reducing the number of treatment modalities is an important part of reducing overall patient morbidity [3]. However,

whenever surgery is considered in place of primary CRT, the possibility of the need for adjuvant therapy always exists. *In order to justify its first-line use, TORS must be shown to either reduce the need for adjuvant therapy altogether, or result in such a low level of morbidity that the additional morbidity of any required adjuvant therapy remains considerably lower than that of primary CRT alone.*

When single-modality surgical treatment is possible, typically consisting of an open neck dissection and TORS resection of the primary, justification of surgery in place of CRT for T1-T2 tumors is relatively straightforward, especially in younger patients with long life expectancies. In cases where adjuvant therapy is likely to be required, such as with clinically node positive (cN+) disease, the advantage of first-line TORS over primary CRT decreases but it is not necessarily eliminated. Assuming adequate surgical margins are achieved and no adverse factors are noted on final pathology, adjuvant RT to the primary site may be completely avoided reducing local complications. Adjuvant RT to the neck may be avoided for N0 or N1 disease without nodal extra-capsular extension (ECE), and the dose may be reduced by 10 Gy or more following complete resection of N2 or higher disease compared to primary CRT. Adjuvant chemotherapy may be avoided altogether in the absence of ECE following definitive surgical excision. For many patients, the avoidance of chemotherapy alone warrants the use of surgery as a first-line therapy, regardless of whether adjuvant post-operative RT is required.

3.6.1.2.2. Advantages of TORS over TOLM and Open Surgery

In centers where trans-oral resections of early pharyngeal and laryngeal tumors have been routine practice by means of TOLM, adoption of TORS must provide advantages that justify its increased costs, specifically in Europe. Here, although the daVinci Surgical System has typically been purchased for other specialties of the same hospital, the use of the EndoWrist instruments, the daVinci-specific drapes, and a fair, time-proportional share of the service and maintenance costs of the robot add up to an extra cost of approximately 1200-1500 Euros per TORS-case. In our inter-departmental billing system, this amount would be billed to the Dept. of ENT. The way we are able to balance these extra, TORS-related costs is that post-TORS patients require less or no

postoperative intensive care (ICU) or intermediate care (IMC) as well as an overall shorter hospital stay compared to those treated with open surgery. In the above mentioned inter-departmental billing system, one night in the ICU costs approximately 800 Euros, billed to the referring department within the hospital. Consequently, if we are able to spare just one ICU night by using TORS in place of open surgery, it compensates already more than the half of the extra, TORS-specific costs. In addition to this, as with all trans-oral approaches, use of TORS avoids the significant surgical access-related morbidity associated with open procedures. Post-operative delay in return to oral intake and ambulation is significantly shortened. Common post-operative complications such as pharyngocutaneous fistulas, infections, and those associated with long-term hospital admissions and major surgeries (deep-vein thrombosis, pulmonary embolism, and pulmonary edema, for example) are significantly reduced.

However, TORS is simply another approach to trans-oral surgery; the daVinci System must be viewed as a surgical tool with its own limitations, and dependent on its operator. The robot will not make one a better surgeon. With this in mind, using the daVinci Surgical System does have significant advantages over TOLM. The TORS learning curve is considerably less steep than that for TOLM [16]. The high-definition, deep depth of field, 3D-view afforded by the robotic endoscope allows for significantly improved tumor visualization. The endo-wristed maneuverability, high degree of freedom and movement scaling afforded by the robotic instruments allows for significantly improved dexterity over TOLM. The line-of-sight, tangential-only cutting, and piece-meal tumor resection limitations of TOLM are eliminated with TORS. This results in a significant increase in the scope of tumors that may be resected trans-orally in an oncologically sound en-bloc fashion (such as large T2 tumors), far beyond that which would be achievable using TOLM.

3.6.1.3. The HPV-Epidemic and TORS

Until community immunity is achieved through vaccination, the incidence of HPV associated HNSCC and the ensuing implications on management will continue to rise. In most advanced centers, biopsies of HNSCC are now routinely tested for evidence of

HPV infection. The two most common tests to detect HPV are p16 protein detection via immunohistochemistry staining and HPV-DNA detection and typing via in-situ hybridization or via a polymerase chain reaction. Not to be confused with the oncogenic HPV-16 viral subtype, the p16 protein is a kinase encoded by the host epithelial cell that acts to block progression from G1 to S phase of the cell cycle. In oncogenic HPV infected cells (HPV16 and HPV18, primarily), p16 protein production is up-regulated due to blockade of p53, p21, and Rb function by the E6 and E7 viral oncogene products.[81] This up-regulation is detected against a p16 antigen, with a sensitivity of 97% and specificity of 84% for detection of E6/E7 protein producing HPV infection.[82] At our institution, patients must also demonstrate HPV-DNA positivity to be classified as having HPV-positive tumors.

Since the HPV HNSCC epidemic was first noted, considerable focus has been placed on the differential response of HPV-associated OPC to radiation therapy (RT). It has been well documented that HPV-driven tumors are more radiosensitive than those driven by DNA damage caused by traditional risk factors such as alcohol and tobacco, in large part due to differences in residual p53 function.[83, 84] There is much debate as to whether radiation doses may be ‘de-escalated’ for patients with tumors demonstrating oncogenic HPV infectivity. However, the simple presence of oncogenic HPV infectivity in a head and neck tumor does not exclude or lessen the possible contributions of other carcinogenic insults on disease progression. Until improved molecular diagnostics are available, HPV infectivity must not be viewed as a favorable feature in the patient with a positive history of prolonged exposure to alcohol and tobacco; HPV is not a ‘cure’ for a tumor that resulted from a lifetime of smoking and drinking. For this reason, the term *HPV-driven* is defined for HPV-positive tumors in patients without classical risk factors for HNSCC. Such tumors must be differentiated from *HPV-associated* tumors, those arising in patients with classical risk factors for HNSCC who also demonstrate tumors testing positive for oncogenic HPV infection.

For patients with HPV-driven tumors, significant improvement in disease specific and overall survival following first-line CRT for OPC has been consistently demonstrated in comparison to those with tumors driven by classical risk factors.[84-87] In many

centers, this evidence has led to the development of a dogma that most – if not all – patients with potentially curable HPV-driven OPC should be managed with first-line CRT. However, this dogma ignores increasing evidence that surgery for HPV-driven tumors offers equivalent, if not improved, survival benefits.[88] Currently there is no evidence to support the first-line use of CRT over surgery for patients with T1-T2 HPV-driven tumors. The fact that HPV-driven tumors are more radiosensitive does not justify the non-consideration of surgery as first-line management. Not only does the younger age and improved general health of patients with HPV-driven tumors make them better surgical candidates, it provides a powerful argument against favoring the use of primary CRT, the morbidity of which tends to increase over time.

4. RESULTS

4.1. Patients with OPSCC

We evaluated the prospectively collected data of 35 OPSCC-patients who underwent TORS at our institution between September 2011 and April 2013 (19 months) as their primary treatment modality. For the detailed description of their tumor status, we refer to the “Patient selection OPSCC” paragraph 2.3.1. above (Table 2). There were 26 males and 9 females, their mean age being 65 years (range 49-84 years). Twelve patients had a positive HPV-status, altogether 11 males and 1 female. Appropriate neck dissections, as warranted upon their cTNM-classification, were performed either in the same operation or as a staged procedure. Following each TORS-resection, all relevant margins were evaluated intraoperatively by frozen section histology, and a robotic re-resection followed during the same session if close or involved margins with invasive cancer or high grade dysplasia (equivalent to carcinoma in situ) were reported by the pathologist.

4.1.1. Preliminary Oncological Outcomes

Completeness of resection (margin status): Clear resection margins were achieved altogether in 33 of the 35 cases (94.3%). In 19 cases, the closest margin was $\geq 5\text{mm}$, which we classify as a well clear margin status. In 14 cases, the closest margin was $\geq 2\text{mm}$ but $< 5\text{mm}$, classified as clear, but close margins. Finally, in 2 cases, the closest margin was $< 2\text{mm}$, which we consider as being potentially involved (Table 7.). The latter was reported on two occasions in the definitive histology, despite the negative frozen sections intraoperatively. These two cases were salvaged surgically within a week following the robotic procedure, with an open re-resection and free flap reconstruction.

Need for adjuvant therapy: After having completed robotic resection followed by their final histopathological report, all patients were re-discussed at the Tumor Board for adjuvant therapy (Table 7.).

Table 7: Early oncologic outcomes of TORS for OPSCC[6]

Measure	No. of patients (%)
Margin status	
Tumor free	33 (94.3)
≥5 mm (well clear)	19
5 mm > M ≥2 mm (close)	14
Potentially involved	
<2 mm	2 (5.7)
Adjuvant treatment vs recurrence	
No indication	13 (37.1)
Recurrence to date	1
Radiation alone (60 Gy)	14 (40)
Recurrence to date	2
Chemoradiation (66 Gy)	5 (14.3)
Recurrence to date	0
Indicated, but refused	3 (8.6)
Recurrence to date	2

Abbreviations: M, resection margin; Gy, Gray.

Adjuvant treatment was completely spared in 13 cases (37.1% of all patients)[59], based on their favorable pTNM-classification and completeness of resection, including neck dissections with a sufficient nodal yield. With one exception, they have all been free of recurrent disease to date. One of them (1/13) presented with a local recurrence 12 months after the robotic resection, which was initially performed with a closest resection margin of 5mm for a T1 N0 oropharyngeal cancer. This patient has ultimately undergone a Re-TORS procedure with repeatedly well clear margins (no dysplasia involved in the new margins).

Fourteen patients received postoperative adjuvant radiotherapy, two of them (2/14) presented with recurrence after 4 and 9 months, with an initial closest resection margin of 5mm and 3mm, respectively; the former was salvaged with an open resection and free flap reconstruction for local recurrence, the latter ultimately deceased of distant metastatic disease. Both of them had a Stage IVA disease at the initial presentation.

Five further patients received postoperative adjuvant chemo-radiotherapy, they have all been free of recurrence to date (0/5).

Finally, 3 patients refused any form of adjuvant treatment recommended by the Tumor Board, and 2 of them developed recurrent disease after 5 and 8 months (2/3), with an initial closest resection margin of 8mm and 5mm, respectively. Both of them had a Stage IVA disease at the initial presentation, and both of them were successfully salvaged with a full-dose chemo-radiotherapy.

Recent follow-up status: At the time of the last follow-up visit (median: 13 months), 30 patients (85,7%) had been recurrent-free (**disease-free survival**, Fig.1.), and altogether 34 patients were alive as well as tumor-free in the same time (**overall survival**, Fig.2.). There had been a total of 5 patients (14.2%) with early recurrent disease, two of them having previously refused adjuvant treatment despite the recommendation of our multidisciplinary head and neck tumor board, but ultimately both of them successfully salvaged with full-dose chemoradiotherapy. One patient died of recurrent disease with distant metastasis (**disease-specific survival**, Fig.3.). Two patients were successfully treated with further surgery (one with Re-TORS and one with open surgery with free flap reconstruction, respectively) for their recurrent oropharyngeal cancer. Among the five patients who developed recurrent disease, only one of them had an initially HPV-driven cancer.

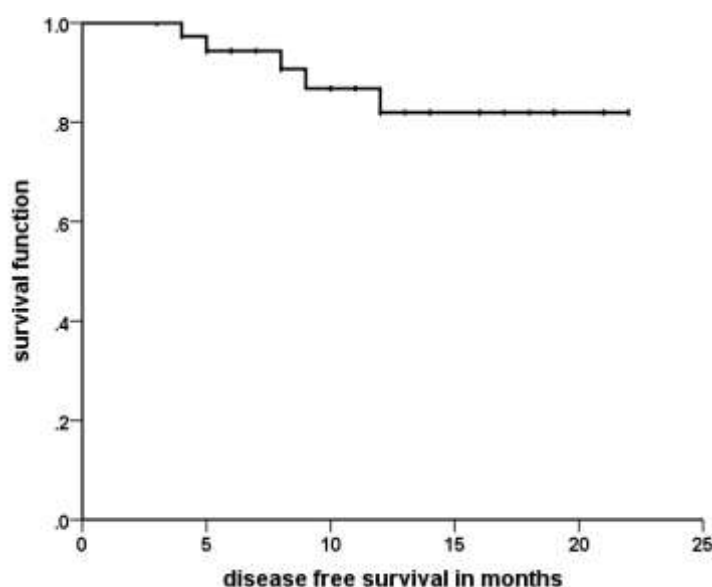


Fig.5: Disease-free survival in months [6]

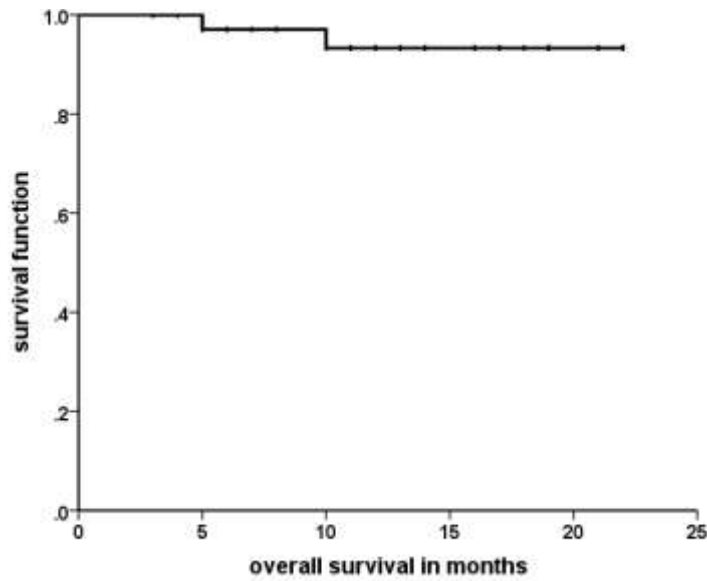


Fig.6: Overall survival in months [6]

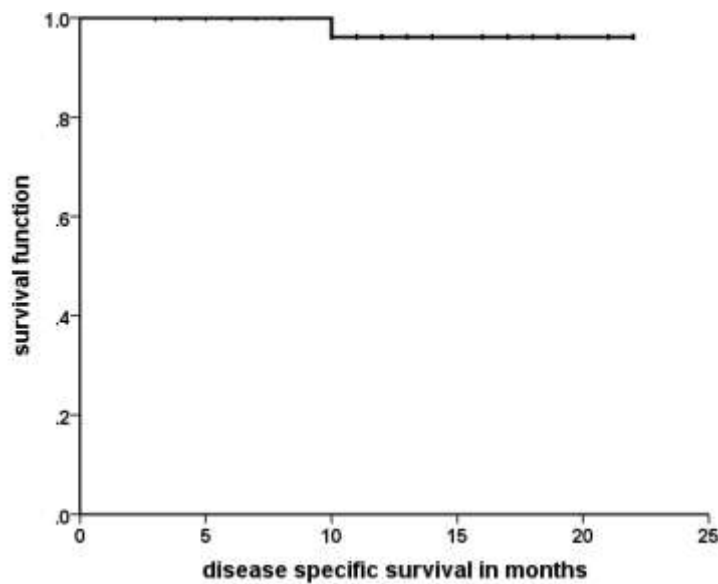


Fig.7: Disease-specific survival in months [6]

Correlation of early recurrence with the initial pTNM-classification, adjuvant therapy, completeness of resection and HPV-status: Out of the five patients who presented with recurrent disease at their last follow-up appointment, four had initially **Stage IVA** disease (**T1 N2a**, with the closest resection margin being 8mm, refused adjuvant therapy, *HPV-driven*; **T1 N2b**, closest margin 3mm, refused adjuvant therapy; **T2 N2b**, closest margin 5mm, received adjuvant radiotherapy of 60Gy; **T2 N2c**, closest margin

3mm, received adjuvant radiotherapy of 60Gy, respectively). Among the patients who developed recurrence, one had initially **Stage I** disease (**T1 N0**, closest margin 5mm) and no adjuvant therapy was offered to this patient (Table 8.). The patient with initially T1 N2a disease was the only one with a positive HPV-status among the 5 patients with recurrence.

Table 8: Subset analysis of recurrences after TORS for OPSCC (5 of 35 patients)[6]

Measure	No. of patients with recurrence (%)
Initial TNM stage	
I	1 (20)
IVA	4 (80)
Initial margin status	
≥5 mm (well clear)	3 (60)
5 mm > M ≥2 mm (close)	2 (40)
HPV status	
Positive/HPV-driven	1 (20)
Adjuvant treatment	
Not indicated	1 (20)
Radiation alone 60 Gy	2 (40)
Refused	2 (40)

Abbreviations: M, resection margin; HPV, human papillomavirus; Gy, Gray.

4.1.2. Functional Outcomes

The outcome measures we used to assess our functional results (Table 9.) were swallowing function represented by the duration of nasogastric tube feeding and/or percutaneous endoscopic gastrostomy (PEG)-feeding, rate of postoperative bleeding, number of elective and emergency tracheotomies, days of intensive care, number of days intubated and days of intermediate care [89].

Swallowing function: None of the patients had a gastrostomy tube at the last follow-up visit, they have all been recently on full oral diet with an acceptable/reasonable to normal physiological swallowing. A nasogastric tube was placed through the non-operated side of the pharynx following the robotic resection still in general anaesthesia, by default in all TORS-patients. The median duration of postoperative nasogastric tube

feeding was 5 days (range: 1 day to 25 days). There were 16 patients who received a PEG-tube: this subgroup consisted of all five patients who received postoperative adjuvant chemoradiation and eleven patients with postoperative adjuvant radiotherapy, with a median duration of 29 days PEG-feeding (range: 7 to 150 days). None of the patients treated with surgery alone needed PEG-feeding.

Elective, temporary tracheotomy was performed at the discretion of the surgeon based on the estimated risk of postoperative upper airway obstruction due to mucosal swelling and the risk of postoperative bleeding, in a total number of 3 patients. The elective tracheotomy was closed within one to two weeks post-TORS, simultaneously with the staged neck dissection(s), if applicable.

Table 9: Functional outcomes of TORS for OPSCC[6]

Measure	No. of patients (%)
PEG dependency	
Long-term	0 (0)
Short-term, median 29 d	
With adjuvant chemoradiotherapy	5 (14.3)
With adjuvant radiotherapy	11 (31.4)
Without adjuvant therapy	0 (0)
NG tube feeding, d, median 5 d	
<7	19 (54.3)
14 >NG ≥7	10 (28.6)
21 >NG ≥14	5 (14.3)
25	1 (2.8)
Tracheotomy, temporary	
Elective	3 (8.6)
Emergency	2 (5.7)
Postoperative bleeding	
Back to OR	2 (5.7)
Postoperative ICU days	
Days intubated	1
IMC days after extubation	1

Abbreviations: PEG, percutaneous endoscopic gastrostomy; NG, nasogastric tube; OR, operating room; ICU, intensive care unit; IMC, intermediate care.

Days intubated, intensive and intermediate care: By default, all TORS patients were kept intubated and have spent the first postoperative night at the intensive care unit (ICU). Extubation followed on the first post-TORS day in the presence of the surgeon, after having observed the resection site and the entire laryngo-pharyngeal mucosa as well as performed a positive leak-test. The median number of days spent in the ICU was 1 day (range: 1 to 5 days), the median number of days intubated was 1 day as well (range: 1 to 2 days). The median number of days spent in the intermediate care (IMC) was also 1 (range: 1 to 3 days).

Postoperative bleeding rate: On two occasions, patients had to be taken back to theatre due to postoperative bleeding from the resection site, on day 1 and on day 6, respectively. These bleedings were stopped using bipolar diathermy and liga-clips.

Emergency tracheotomy was performed to the patient who presented with postoperative bleeding on day 1, and for another patient due to upper airway obstruction on the basis of delayed swelling of the pharyngeal mucosa on day 6. These tracheotomies were also closed within one to two weeks.

4.2. Patients with HPSCC

The median age of the patients was 64 years. There were four males and one female patient. There were two p16-positive tumours, only one of those being HPV-DNA positive in the same time. The patient presented with the latter tumour was a life-long non-smoker and non-drinker, supporting the theory that HPV can play a role outside of the oropharynx as well. Preoperatively, three tumours were classified as cT1 and two as cT2, and one of the cT1 tumours was pathologically upstaged to pT2 postoperatively. Following their TORS-procedure, they all underwent an ipsilateral selective neck dissection including levels IIa, IIb, III and IV in a concurrent fashion; total nodal yield was over 20 in each case. Despite recent recommendations regarding Level IIb in a cN0 neck, we did harvest the entire Level II in these patients in order to maximize nodal yield and stay oncologically as safe as possible even without adjuvant treatment.

4.2.1. Preliminary Oncological Outcomes

Completeness of resection (margin status): Clear resection margins were achieved in all cases. In four patients, the closest margin was $\geq 5\text{mm}$, which we classify as a well clear margin status [18]. In one single case, the closest margin was 4mm (Table 4).

Need for adjuvant therapy: After having undergone robotic resection followed by their final histopathological staging, all patients were re-discussed at the Tumour Board for adjuvant therapy. Adjuvant treatment was completely spared in 3 cases, based on their favourable pTNM-classification and completeness of resection, including neck dissections with a sufficient nodal yield. One patient received adjuvant radiation alone (60 Gy) for his pT2 pN0 hypopharyngeal cancer, based on adverse features shown in his final histology such as poor differentiation, as well as perineural and lymphovascular invasion. One patient received 66Gy adjuvant chemoradiotherapy for his pT2 pN2b disease, which may question the necessity of the surgery [90], being almost as much as a primary chemoradiation of 70Gy. In his case, we indicated the surgery hoping to spare him 10Gy of radiation and the chemotherapy component of the adjuvant treatment, without radiologically suspected nodal extracapsular spread (ECS) in the neck. The latter feature was nevertheless evident in the final histology, so an adjuvant chemotherapy had to be included with the radiation increased up to 66Gy (Table 10).

Recent follow-up status: At the time of their last follow-up visit (median: 18 months), all patients had been recurrent-free and altogether four patients were alive as well as tumor-free in the same time. One patient died of other disease (heart attack). Their early oncologic outcomes with their last follow-up status are summarized in Table 10.

Table 10.: Oncologic and functional results following TORS for HPSCC[25]

Patient no.	#1	#2
Adjuvant th.	No	CRT 66 Gy
Recurrence	No	No
Follow-up (median 18 months)	28 months	5 months
Current status as of June 2014	Alive, tumour free	Died of other disease (5 months postop)
FEES 1 w. postop.	No penetration or aspiration	Mild aspiration
FEES 3 m. postop.	No penetration or aspiration	Severe aspiration
FEES 6 m. postop.	No penetration or aspiration	N/A

Cont'd. Table 10.: Oncologic and functional results following TORS for HPSCC[25]

#3	#4	#5
RT 60 Gy	No	No
No	No	No
19 months	18 months	14 months
Alive, tumour free	Alive, tumour free	Alive, tumour free
No penetration or aspiration	Severe aspiration	No penetration or aspiration
Mild aspiration	Mild penetration	No penetration or aspiration
No penetration or aspiration	No penetration or aspiration	No penetration or aspiration

Abbreviations:

CRT: chemoradiotherapy

RT: radiotherapy

FEES: Functional Endoscopic Evaluation of Swallowing

4.2.2. Functional Outcomes

No conversion to open surgery was necessary. Blood loss was minimal in all cases [62]. Mean robotic setup time was 31 minutes (range: 16-48 minutes). Because of the rather horizontal retractor angle required for the hypopharyngeal access, edentulous patients were considerably easier to set up. Once the retractor was in position, docking of the robotic arms took an additional 18 minutes (mean; range: 8-22 minutes). The robotic-assisted resection itself, i.e. the mean console time was 44 minutes (range: 27-59 minutes) [16]. All patients underwent an ipsilateral selective neck dissection (levels II-IV) in a concurrent fashion. The outcome measures we used to assess our functional results were swallowing quality represented by the duration of nasogastric tube feeding and/or PEG-feeding, rate of postoperative bleeding, number of elective and emergency tracheotomies, days of intensive care, number of days intubated and days of intermediate care [91] (Table 4).

Swallowing function: Median duration of nasogastric tube feeding was 5.5 days (range: 3-18 days). One of the patients (patient Nr.4.) with a recurrent hypopharyngeal tumor after primary chemoradiation, had a PEG-tube prior to surgery, as she developed severe dysphagia during and after her conservative treatment which made her long-term PEG-dependent. In her case, TORS was used for salvage surgery [92]. Another patient (patient Nr.2.) received a PEG-tube on the 18. postoperative day, because he needed adjuvant chemoradiation and his already impaired swallowing function was expected to deteriorate further during his adjuvant treatment. All other patients resumed full oral diet within the first postoperative week with a reasonable to normal physiological swallowing [93]. Functional endoscopic evaluation of swallowing (FEES) was carried out at 1 week, 3 months and 6 months postoperatively (Table 10.).

Elective, temporary tracheotomy was performed in one case (patient Nr.3.) due to postoperative mucosal swelling and difficult intubation in the anamnesis. The tracheotomy was closed on the 6. postoperative day. However, possible arguments for a routinely performed elective tracheotomy in hypopharyngeal and supraglottic TORS-cases are detailed in the *Discussion*.

Days intubated, intensive and intermediate care: By default, initially all our TORS patients were kept intubated for 24 hours and have spent the first postoperative night at the ICU. Extubation followed on the first post-TORS day in the presence of the surgeon, after having observed the resection site and the entire laryngo-pharyngeal mucosa as well as performed a positive leak-test.

Postoperative bleeding rate: In this subgroup of patients, there was neither any postoperative bleeding nor need of an emergency tracheotomy.

4.3. Neck Dissection Outcomes

Harvested lymph node counts from Group 1 and Group 2 were compared in two categories: 1.) Nodal count comparison per neck level, and 2.) Overall nodal yield from the entire neck.

4.3.1. Statistical analysis

4.3.1.1. Harvested lymph node count comparison per neck level

The mean harvested lymph node count *per level*, irrespective of which level it is, was **5.89** with a 95% CI ranging from 5.33 to 6.44 in Group 1, and **3.90** with a 95% CI ranging from 3.47 to 4.33 in Group 2, representing a mean difference of 1.99 lymph nodes per level ($p < 0.001$).

The comparison of mean harvested lymph node counts broken down into each individual neck level (Fig.8.) gave the following results:

Level I: **3.38** with a 95% CI ranging from 2.74 to 4.01 in Group 1, and **1.67** with a 95% CI ranging from 0.99 to 2.35 in Group 2, representing a mean difference of 1.75 lymph nodes ($p < 0.001$).

Level II: **6.80** with a 95% CI ranging from 5.89 to 7.71 in Group 1, and **4.61** with a 95% CI ranging from 3.87 to 5.36 in Group 2, representing a mean difference of 2.23 lymph nodes ($p<0.001$).

Level III: **6.06** with a 95% CI ranging from 5.23 to 6.89 in Group 1, and **3.77** with a 95% CI ranging from 3.14 to 4.40 in Group 2, representing a mean difference of 2.33 lymph nodes ($p<0.001$).

Level IV: **6.17** with a 95% CI ranging from 5.30 to 7.03 in Group 1, and **3.74** with a 95% CI ranging from 3.11 to 4.38 in Group 2, representing a mean difference of 2.43 lymph nodes ($p<0.001$).

Level V: **5.34** with a 95% CI ranging from 4.01 to 6.67 in Group 1, and **5.49** with a 95% CI ranging from 4.32 to 6.66 in Group 2, representing a mean difference of -0.13 lymph nodes ($p=0.868$, **not significant**)

The nodal yield advantage of Group 1 patients was highly significant in Levels I, II, III and IV, while the differences in Level V were not significant.

4.3.1.2. Overall nodal yield

In Group 1, the mean overall nodal yield from one side of neck was **22.53**, with a 95% CI ranging from 20.43 to 24.63. In Group 2, the mean overall nodal yield from one side of neck was **15.00**, with a 95% CI ranging from 13.37 to 16.63 (Fig.9.). The mean difference of 7.53 lymph nodes between the two groups is significant ($p<0.001$).

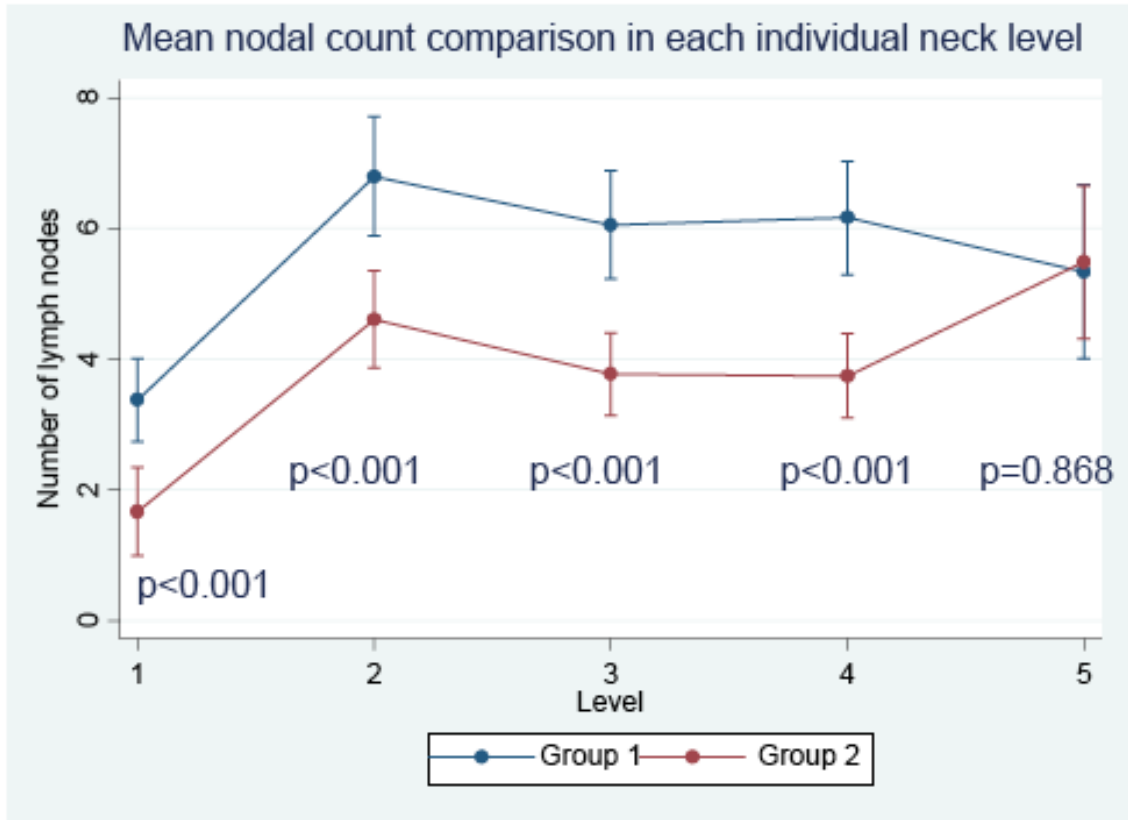


Fig.8: Nodal yield per neck level

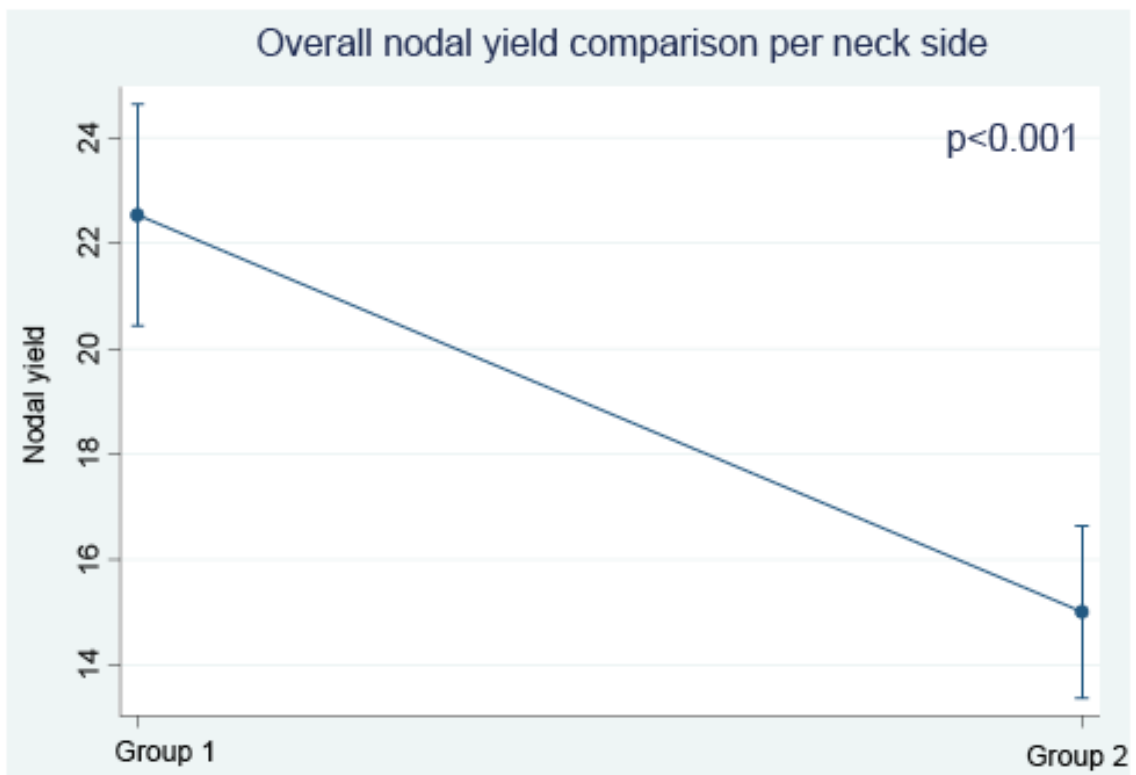


Fig.9: Nodal yield per neck side

4.3.2. Timing of Neck Dissection in Patients Undergoing TORS

4.3.2.1. Pattern of Spread

Histopathological examination of the neck dissection specimens revealed pN-positive status in 12 (57.1%) patients of the control group, versus 15 (75%) patients of the experimental group. None of the patients in the control group showed histologically confirmed lymph node metastasis in level I, whereas one (5%) patient had a single positive lymph node in level I in the experimental group (Table 6).

In 12 (57.1%) patients, the ipsilateral level II was determined as the primary lymphatic region of metastatic spread in the control group, versus 11 (55%) patients with a similar pattern of spread in the experimental group (Table 6).

4.3.2.2. Nodal Yield

Nodal yield is defined as the overall number of harvested lymph nodes in a regional lymphadenectomy. In the control group, 574 lymph nodes were harvested from 86 dissected levels in the ipsilateral neck dissections, resulting in a nodal count of 6.7 per level. The nodal yield per neck side was 27.3 in the control group. In the experimental group, altogether 577 lymph nodes were harvested from 73 dissected levels in the ipsilateral neck dissections, resulting in a nodal count of 7.9 per level. The overall nodal yield per neck side was 28.9 in the experimental group. The difference between the overall nodal yield values of the two groups was not significant (Table 11).

The nodal yield values broken down into each individual neck level are also listed in Table 11. Differences between the control group and the experimental group were not significant in levels I, II and III. The only significant difference in terms of nodal count between the two groups was observed in level IV, where more lymph nodes were harvested from patients in the experimental group than from those in the control group.

Table 11.: Comparison of nodal yield vs. the timing of neck dissections

	No. of LN harvested		No. of levels dissected		nodal yield per level		
	control	experimental	control	experimental	control	experimental	p value
Level I	65	43	18	10	3.6	4.3	0.5501
Level II	185	165	21	20	8.8	8.3	0.7462
Level III	149	140	21	20	7.1	7.0	0.9443
Level IV	142	214	21	20	6.8	10.7	0.0227
all other levels	33	15	5	3	6.6	5.0	0.5183
ipsilateral neck	574	577	86	73	27.3	28.9	0.6571

Abbreviations: LN = lymph node

4.3.2.3. Intraoperative Complications

During the concurrent and staged ipsilateral neck dissections, levels Ib and IIa were assessed for through-and-through communication, or pharyngocervical fistula formation. In the control group, two (9.5%) fistulae could be located versus one (5%) fistula in the experimental group (Table 12).

All defects were primarily closed at the end of the procedure by placing myo-mucosal sutures into the pharyngeal constrictor muscles as well as by reconstruction using a pedicled local muscle flap of the digastric, omohyoid or sternocleidomastoid muscles, whichever was more convenient for the given defect in the given patient. Fibrin glue was not used in any of the cases.

Patients received i.v. antibiotic coverage for 7 days with cefuroxim or clindamycin for having undergone clean-contaminated surgery due to pharyngocervical communication.

4.3.2.4. Postoperative Complications

Following TORS, patients were kept intubated for one night at the intensive care unit to prevent the possible consequences of mucosal swelling and/or postoperative bleeding, except those cases managed with elective temporary tracheotomy, which was only performed in a few selected high-risk patients [6].

Postoperative pharyngocutaneous fistula did not occur in any of the patients, irrespective of the timing of their neck dissection (Table 12). In the control group, one patient (4.8%) had a postoperative bleeding from the ipsilateral neck dissection site, and

two (9.5%) patients had postoperative bleeding from the primary TORS-resection site. Hemostasis has been achieved under general anaesthesia in each of those cases.

In the experimental group, no bleeding occurred either from the neck or from the primary resection site. Other postoperative complications, such as hematoma, seroma and infection were documented and are listed in Table 12. The differences between the two groups were not significant in any regard.

Table 12.: Comparison of complication rates vs. the timing of neck dissections

Variable	control group	experimental group	
	No. of patients (%)	No. of patients (%)	p value
Cohort	21	20	
Intraoperative complications			
pharyngocervical fistula	2 (9.5)	1 (5.0)	0.2947
Intraoperative reconstruction			
local muscle flap	2 (9.5)	1 (5.0)	0.2947
Postoperative complications			
fistula	0	0	
bleeding neck	1 (4.8)	0	0.1677
bleeding primary site	2 (9.5)	0	0.0825
hematoma	2 (9.5)	0	0.0825
seroma	0	1 (5.0)	0.1558
infection	0	0	

Abbreviations: ND = neck dissection

4.4. Our Concept for TORS

As a result of all the above considerations, we attempted to outline the points to follow when recommending TORS as the primary treatment for head and neck cancer patients, as shown in Table 13:

Table 13.: Step-by-step evaluation of potential TORS-candidates

4.4.1. Selecting the ideal TORS candidate:

1. The patient has no general contraindications to surgery
2. The primary tumor is functionally well resectable, without significant long-term impairment
3. There is no radiological sign of ECE
4. Clear surgical margins (≥ 2 mm) are likely to be achieved for the primary tumor, ideally well clear (≥ 5 mm) margins are to be expected
5. Surgery is likely to result in the reduction or elimination of adjuvant CRT

These considerations have also resulted in creating the following decision framework for head and neck cancer primary treatment at our institution, as shown in Table 14.

Table 14.: Decision algorithm for primary treatment of HNSCC patients

cT classification	cN classification	Radiologically suspect ECE	Preferred treatment option
T1 or T2	N0 or N1	negative	TORS with SND +/- RT 60 Gy
T1 or T2	N2 or N3	negative	TORS with SND or mRND and RT 60 Gy
T1 or T2	any N-positive	positive	Primary CRT 70 Gy +/- ICT
T3 or T4	any N	negative	Conventional surgery with SND or mRND and RT 60 Gy or Primary CRT 70 Gy +/- ICT
T3 or T4	any N-positive	positive	Conventional surgery with mRND or RND and CRT 66 Gy or Primary CRT 70 Gy +/- ICT

Abbreviations:

ECE: extra capsular extension

TORS: trans oral robotic surgery

SND: selective neck dissection

mRND: modified radical neck dissection

RND: radical neck dissection

RT: radiotherapy

CRT: chemo-radiotherapy

ICT: induction chemotherapy

Gy: Gray

5. DISCUSSION

5.1. Oropharyngeal SCC

Transoral robotic surgery has several advantages over conventional endoscopic surgery of the upper aerodigestive tract, including trans oral laser microsurgery (TOLM). The latter provides with a tangential-only cutting plane due to the known line-of-sight issue, while a constant repositioning of the laryngoscope is often still necessary. As a consequence of these limitations, en bloc resection is not possible in many cases and a piece-meal technique is considered to be acceptable by a number of authors [90].

In contrast to TOLM, TORS has an ability to perform multi-planar en-bloc tumor resections under a magnified 3D-HD-view, which enables the assessment of the resection margins to be more accurate. The greater degree of freedom of the Endowrist-instrumentation makes the margin safety of the resections equally sound to that of conventional open surgery, but on a much lower cost of surgical morbidity. This, paired with a histopathologically most reliable margin assessment due to the en bloc resection, allows TORS to match the oncological safety of open surgery with the low morbidity of endoscopic laser surgery [90].

From a functional point of view, numerous clinical studies have shown improved post-TORS swallowing function compared to other surgical modalities and to primary chemoradiation therapy, along with shorter hospital stay and faster recovery, as well as a more efficient return to work after completion of therapy [91]. However, the overall hospital stay may be longer than TORS alone would allow it to be, due to simultaneously performed neck dissection(s). If the neck dissection(s) are planned in a staged fashion, the patient has to undergo surgery and general anesthesia twice. Faster recovery means that adjuvant therapy, if indicated, may start sooner, which improves locoregional control.

If TORS is going to succeed mid-term and long-term, its current indication field may need to be expanded, in order to allow select tumors with higher T-classification to be

treated transorally under well-defined conditions. One possibility would be a preoperative downstaging of the primary disease by administering induction chemotherapy prior to surgery. With a good response rate, this would allow to resect originally larger tumors with well clear margins and to obtain a reliable surgical staging of the neck by performing neck dissection(s) in a concurrent fashion. This combination may allow de-escalation of adjuvant treatment in patients who responded well to induction chemotherapy as well as had favourable histopathological parameters following TORS for their primary along with staging neck dissection(s) with a sufficient nodal yield [58].

Another possibility to selected treatment de-escalation would be to differentiate between the simply p16-positive cases and the truly HPV-driven cases. In our present study, HPV-status vs. HPV-drivenness are represented by the following figures: out of the 35 oropharyngeal squamous cell cancer (OPSCC) patients treated primarily (or even solely) with TORS, 18 showed p16-positivity with immunohistochemistry (51.4%). In many, especially overseas studies, they would have been automatically considered as being genuinely HPV-positive, which is not necessarily the case, as p16 is only a surrogate marker and can be positive for other reasons as well [94]. As we went further, HPV-DNA-testing showed positivity in only 12 cases of the eighteen p16-positive patients (34,3% of all 35 patients). In our definition, they have had the true HPV-positive tumors (positive *HPV-status*). Whether their positive HPV-status was the main causative agent in developing their OPSCC, can be better estimated by looking at their smoking and drinking habits, as other possible causative factors. Taking the latter into consideration, only 9 patients fulfilled our criteria of having smoked less than 10 pack years and not consuming alcohol on a regular basis (25.7% of the 35 OPSCC-patients), and they are the ones having truly *HPV-driven* tumors in our opinion, not only a positive *HPV-status*[95].

5.2. Hypopharyngeal SCC

Specifically in the hypopharynx, transoral robotic surgery has several advantages over transoral laser microsurgery. The latter provides with a tangential-only cutting plane because of the known line-of-sight issue, while a constant repositioning of the laryngoscope is often necessary. As a consequence of these limitations, en bloc resection is not possible in many cases and a piece-meal technique is considered to be acceptable by a number of authors. To illustrate the access advantage of TORS over TOLM, Fig.10a and Fig.10b show the tumour of Patient Nr.1., being exposed first with a conventional Kleinsasser-B-laryngoscope, suitable for TOLM. The laryngoscope has to be repositioned to expose either the inferior, or the superior portion of the tumour, on Fig.10a and on Fig.10b, respectively. In contrast to this, the LARS retractor system, specifically designed for TORS, makes it possible to expose the entire tumor in a single position, shown on Fig.11.

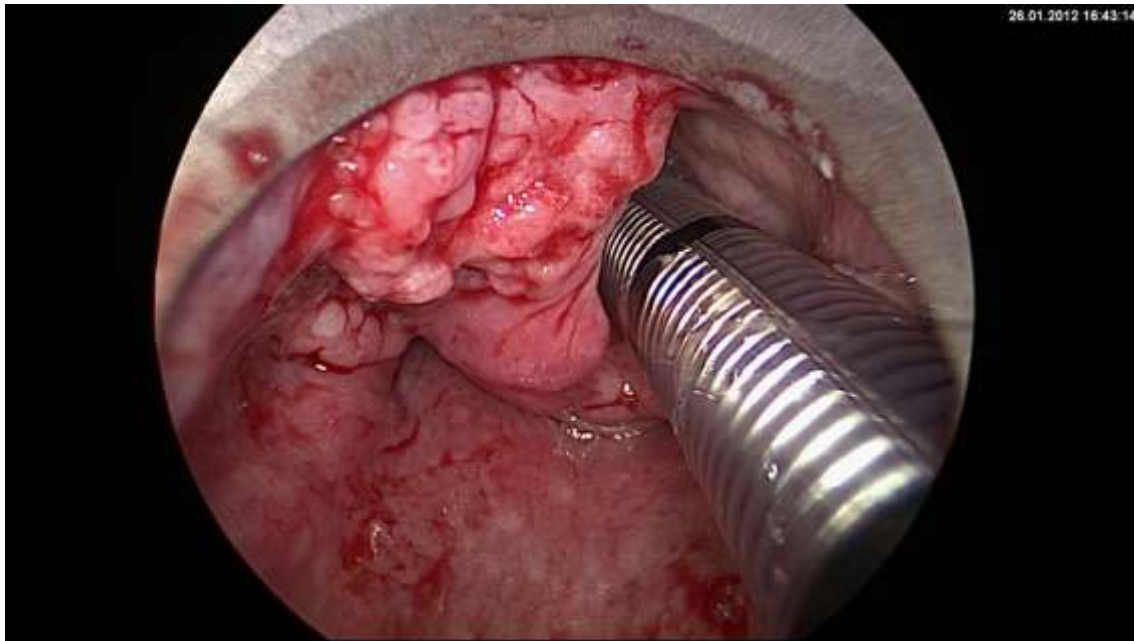


Fig.10a: Left piriform fossa / aryepiglottic fold tumour exposed with the Kleinsasser-B-scope, showing only the inferior portion of the tumour [25] photo by BBL

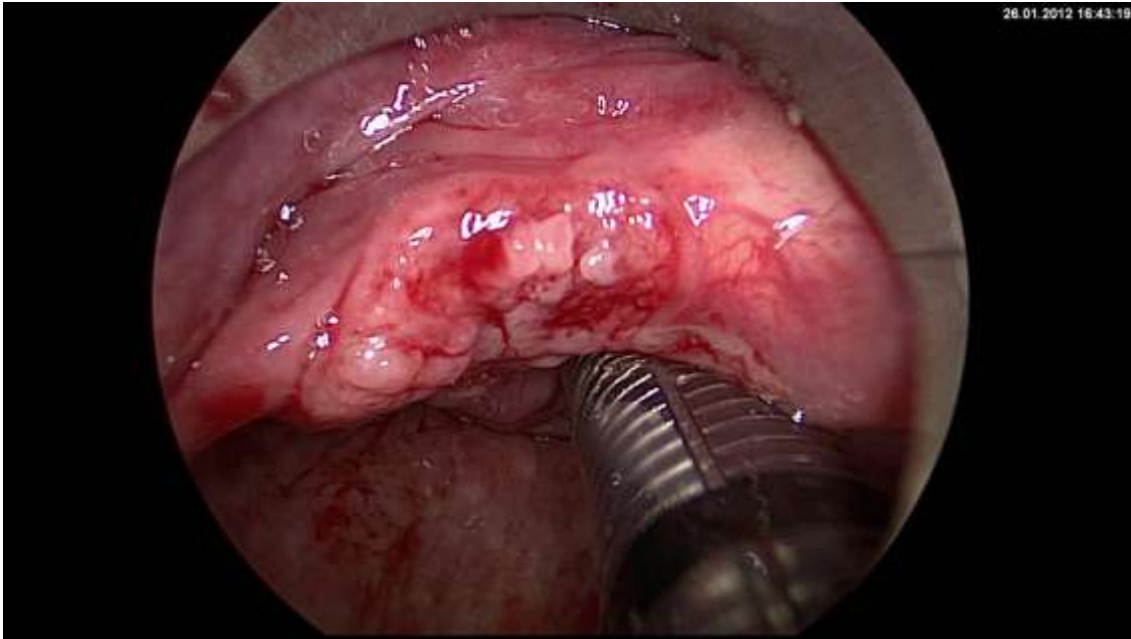


Fig.10b: Left piriform fossa / aryepiglottic fold tumour exposed with the Kleinsasser-B-scope, showing only the superior portion of the tumour [25] photo by BBL



Fig.11: Left piriform fossa / aryepiglottic fold tumour exposed in its entirety with the LARS retractor system. No need for intraoperative repositioning [25] photo by BBL

As a consequence of this, TORS enables the surgeon to perform multi-planar en-bloc tumor resections under a magnified 3D-HD-view even in confined spaces like the hypopharynx, which allows a more accurate assessment of the resection margins. The greater degree of freedom of the Endowrist-instrumentation makes the margin safety of the resections equally sound to conventional open surgery, but on a much lower cost of surgical morbidity. This allows TORS to match the oncological safety of open surgery with the low morbidity of endoscopic laser surgery.

Among our first fifty TORS-cases, consisting of predominantly oropharyngeal cancer patients but also including this subset of five hypopharyngeal cases presented here, there were two postoperative bleedings that required intervention under re-intubation (4%), and neither of those occurred from the hypopharynx. Although elective tracheotomy was not performed routinely in our series, the authors would like to emphasise that any bleeding in the hypopharynx or in the supraglottic larynx can be potentially life-threatening by preventing re-intubation and blocking the airway. Therefore, performing an elective tracheotomy in hypopharyngeal and supraglottic TORS-cases may be reasonable in our opinion, especially if no neck dissection is done during the same session.

In our series, all patients underwent an ipsilateral selective neck dissection in the same time, with subsequent ligatures of the ascending pharyngeal and lingual arteries, to reduce the risk of postoperative bleeding from the hypopharyngeal primary TORS-resection site. However, in cases with a staged (delayed) neck dissection, we would recommend performing an elective tracheotomy even before starting the robotic resection, in order to remove the endotracheal tube from the surgical field for a better access as an extra benefit, in addition to securing the airway postoperatively.

5.3. Neck Dissection

5.3.1. Explaining Level V

There are two aspects to explain why the differences in Level V were not significant. First, in our patient cohort, there were a lot less neck dissections including Level V than including other levels, so there may be a low sample size issue when evaluating isolated results from Level V. Most selective neck dissections does not include Level V. Second, the fascia unwrapping technique affects primarily Levels II, III and IV in the N0 neck, as the plane of dissection starts to be developed along the leading edge of the sternomastoid muscle, so the nodal yield advantage might be concentrated to these lateral levels and may not be so much present in Level 5.

5.3.2. General Considerations

In the light of the current human papilloma virus (HPV) epidemic, application of intensity modulated radiotherapy (IMRT) and trans oral robotic surgery (TORS) [95], the emphasis is more on the quality of life today, and we have more data on the long-term sequelae after 70-72 Gy primary chemoradiation than previously. It became also evident that the overall better prognosis of HPV-positive oropharyngeal squamous cell cancer (OPSCC) is applicable *irrespective of the treatment modality* [96], i.e. it applies to surgery as primary treatment as well [97-99]. In 2009, the Food and Drug Administration (FDA) approved TORS for T1 and T2 malignancies of the head and neck, opening the gate for a new paradigm shift taking currently place, moving back towards surgery in a minimally invasive, robotically assisted manner. In this scenario, aiming for an overall less toxic treatment package [94], the quality of the performed neck dissections is of paramount interest, both from a treatment-related morbidity and from an oncological aspect.

In a therapeutic setting with a cN+ neck, it is still safe to perform functional and selective neck dissections with unwrapping the cervical fascia, as long as there is no macroscopic ECS. In an elective cN0 setting [100], improved nodal yield increases the

reliability of the information provided by the neck dissection specimen. This is of utmost importance when a decision on omitting adjuvant therapy relies on the pN0 information based on an electively performed neck dissection.

When balancing oncological safety with improved quality of life, it is especially important to identify those low-risk patients who may do just as well without any adjuvant treatment [101], e.g. the *truly* N0-patients. For these patients, the importance of a reliable surgical staging of the neck cannot be emphasized enough, as it serves as the basis of their management.

Nodal yield and lymph node ratio are known to have a prognostic value in oral [40, 43] and in oropharyngeal [102] squamous cell carcinoma. The number of harvested lymph nodes did not differ significantly between the two groups in levels I, II and III. Level IV was the only level where a significant difference has been shown, although this level is not relevant with regards to the main question of this study, as intra- or postoperative pharyngocervical fistula formation is only expected in levels Ib and IIa after TORS. The latter outcome measures did not show a significant difference either. Despite the fact that most patients with a pN-positive neck status had their metastatic disease in level II, this circumstance did not increase the rate of fistula formation. In the same time, our low fistula rate did not compromise nodal yield.

In the present context, besides concurrent or staged neck dissections, there is also a third option of performing the neck dissection prior to the TORS-procedure. This would merge some of the advantages of the two other options: it provides with a pre-TORS opportunity to ligate the relevant branches of the external carotid artery, should this be the preference of the surgeon; it would presumably decrease the risk of pharyngocervical fistula formation; and, it would allow for more convenient theatre list planning in certain hospitals and health systems.

There are several reasons why we did not include this third option into our comparison. First, we only did it five times, because we generally prefer to remove the primary tumour at the earliest convenience to prevent (further) metastatic spread – ideally within two weeks after the initial diagnosis.

Second, even after a very thorough neck dissection with a high nodal yield, there are most likely always a few lymph nodes still left behind that may harbour new micrometastatic cells from the primary tumour until the TORS-procedure has been done. A neck dissection prior to the resection of the primary tumour may change the pattern of spread of the latter, and the physical manipulation during the delayed TORS-procedure in the primary site may also release further tumour cells into the lymphatic system, that will no longer be treated if there is no indication for adjuvant treatment due to favourable tumour stage.

Third, we always book the first available robotic theatre slot for our new cancer patients, as this is the rate-limiting step within our treatment algorithm, because booking the neck dissection is much less specific (in terms of surgeon, theatre, available scrub nurses etc.) and therefore much faster afterwards.

5.4. TORS Concept

If TORS is chosen as first-line treatment for HNSCC, oncological principles of en bloc resection and generous margins must be maintained, while preserving satisfactory function. Neither clear surgical margins nor organ function may be compromised on the account of preferring one over the other. Adjuvant CRT is not a solution for oncologically insufficient surgery; whenever TORS is offered as first-line therapy, one must reasonably expect that post-operative adjuvant therapy will either not be required or that the dose requirements will be significantly less than what is required for primary CRT. In the same way, when addressing the neck in TORS patients, nodal yield must be maximized while surgical morbidity minimized.

In moving forwards, the role of TORS in the treatment spectrum of HNSCC must be considered in a geographical context. Being clearly less morbid than open surgery, TORS has rapidly gained field in the U.S. against primary CRT, the latter being the only other broadly accepted treatment. In Europe, where TOLM has long been widely established as a reasonable alternative to primary CRT, TORS has been slower to gain a foothold. However, as recognition of the technical advantages of TORS over TOLM increases, use of TORS in Europe will certainly expand. With time and competition,

economic barriers to the use of TORS will begin to decline. The HPV HNSCC epidemic disproportionately affecting younger and healthier patients will only serve to increase the use of the minimally invasive and function-conserving TORS approach when it allows for the reduction or elimination of the need for highly morbid CRT.

Finally, if TORS is to succeed on a larger scale in the management of HNSCC, its current indications must be expanded. At present, the daVinci Surgical System is only approved for resection of T1 and T2 head and neck cancer; its use for the resection of larger or more invasive upper aero-digestive tract malignancies is strictly off-label, technically more challenging, and could be expected to result in more significant post-operative functional impairment and complications. One possible means to expand the reach of TORS may be through the use of induction chemotherapy; T3 tumors that demonstrate a response might then become candidates for TORS.

6. CONCLUSIONS

6.1. OPSCC

Based upon our functional results and margin control rates, we found TORS to be an oncologically safe and technically feasible surgical modality. It widens our treatment portfolio by providing with a novel minimally invasive surgical alternative to select head and neck cancer patients, especially to those with T1 and T2 primary disease of the upper aerodigestive tract, with promising functional results.

While it is difficult to assess components of the cumulative morbidity of combined treatment separately, it is of note that all patients with PEG-feeding did receive some form of adjuvant therapy, and none of the patients treated with surgery alone (TORS and neck dissection) needed PEG. One of the largest prospective, oropharyngeal post-TORS quality of life studies [22] also showed TORS to be safe with excellent overall QoL and functional outcomes, even in patients undergoing adjuvant radiotherapy. In the latter group, after an initial drop in their post-treatment QoL-scores, overall QoL returns to baseline values by 12 months post-TORS.

These seem to support our original premise that the overall morbidity of TORS and adjuvant therapy might be in well selected cases lower than the morbidity of primary chemoradiation. In the future, we think the emphasis of minimally invasive head and neck surgery will be shifted towards the HPV-driven patient population, which trend is not represented in our current set of data yet, but is to be certainly expected.

Being TORS a relatively new technique worldwide, the number of studies presenting longer term results are still very limited. Based upon our early oncological and functional outcomes, we are convinced that further clinical investigations are justified and continued efforts to decrease the overall treatment-related morbidity of the multimodality therapy of head and neck squamous cell carcinoma are encouraged. In this scenario, TORS will most likely play an integral role as one of the leading modalities.

6.2. HPSCC

From a functional point of view, numerous clinical studies have shown improved post-TORS swallowing function compared to other surgical modalities and to primary chemoradiation therapy [91, 93], along with shorter hospital stay and faster recovery, as well as a more efficient return to work after completion of therapy [22, 78].

We found TORS to be an oncologically safe, technically feasible surgical modality for select T1 and T2 hypopharyngeal squamous cell carcinomas [80], with excellent margin control and minimal morbidity. Paired with an equally low-morbid selective neck dissection with sufficient nodal yield, the goal is to spare adjuvant treatment for a select group of low-risk patients.

However, in cases where adjuvant therapy cannot be completely omitted, we find a reduction of at least 10-12 Gy in radiation (from 70-72 Gy of first-line conservative treatment to 60 Gy of adjuvant treatment) and sparing the chemotherapy component of adjuvant therapy, are worth indicating TORS and selective neck dissection for well accessible T1 and T2 hypopharyngeal carcinomas [80, 103], in order to improve their functional outcomes compared to first-line chemoradiotherapy [77, 79].

5.3. Neck Dissection

Our study showed that a certain surgical concept and the standardised dissection technique derived from it, can deliver superior results in terms of nodal yield and may increase the overall oncological safety. It is remarkable that the horizontal technique, even as a freshly implemented method in this department, can produce reliably higher nodal yield values than the already well-established vertical technique.

In an era of constantly growing health care costs, a simple change in the surgical mindset and dissection technique might contribute just as much to the oncological benefit of the patients as high-tech developments do, making a difference any surgeon can make without financial offset.

In conclusion, our study showed that the timing of the neck dissection in patients undergoing TORS does not have an impact on the outcomes. We still believe that neck dissections should be done as soon as possible following the TORS-procedure, ideally during the same session, as there is no reason to delay a neck dissection if it can be done on the same theatre list. On the other hand, appropriately indicated TORS-cases should not be restricted due to robotic slot and theatre time constraints, as TORS might be the ideal primary treatment option for a number of patients, even if the neck dissections cannot be done on the same day. In our experience, either way is feasible and leads to similar outcomes.

5.4. TORS Concept

As with any novel therapy, it is paramount that prospective multicenter randomized trials are able to confirm the safety and efficacy of TORS in the first-line management of HNSCC. These studies must be designed around the unique advantages and limitations of the daVinci Surgical System in TORS; proper patient selection within such studies is vital. We believe that the advantages offered by TORS over conventional treatment modalities applied on a wide scale will result in a paradigm shift in the QOL outcomes of head and neck cancer patients. However, further, higher level confirmatory evidence is needed for the growth of TORS in the management of HNSCC.

7. SUMMARY

Background

The multimodality treatment arsenal for head and neck squamous cell carcinoma has been recently supplemented by transoral robotic surgery (TORS). The purpose of this work was to introduce TORS and to define its role as part of the multidisciplinary treatment spectrum of head and neck oncology, based on the author's clinical and surgical experience of over a hundred robotic cases, publications, as well as international teaching practice as a proctor and trainer in this regard.

Methods

TORS has been applied for the treatment of the primary tumours in the oropharynx and hypopharynx, while functional and selective neck dissections were used for the surgical treatment as well as for the staging of the regional lymph nodes in the neck, according to the approval of the institutional head and neck tumour board.

Results

So far the highest surgical monomodality treatment rates previously unmatched in the published literature, without adjuvant therapy. Comparable short-term (median, 2 years) oncological outcomes to that of primary chemoradiation, with improved functional results. First evidence for the impact of neck dissection surgical technique on the harvested nodal yield as an independent prognostic factor. First standardised, TNM-stage related treatment algorithm for the application of TORS in head and neck oncology.

Conclusions

TORS with functional and selective neck dissection and risk-adapted adjuvant therapy is able to match the oncologic outcomes of primary chemoradiation for T1 and T2 HNSCC, possibly on a lower cost of treatment-related morbidity.

8. ÖSSZEFOGLALÁS

Bevezetés

A fej-nyaki rosszindulatú daganatok multidiszciplináris terápiás arzenálja a közelmúltban bővült a transzorális robotsebészet (TORS) nyújtotta lehetőségekkel. A disszertáció célja a fej-nyaki robotsebészet bemutatása és szerepének meghatározása a fej-nyaki onkológia multidiszciplináris terápiás spektrumának új tagjaként, a szerző saját ezirányú műtéti tapasztalatai (több mint 100 TORS-beavatkozás), publikációi és nemzetközi TORS-oktatói tapasztalatai alapján.

Módszer

TORS a primér tumor kezelésére (oropharynx és hypopharynx), funkcionális és szelektív nyaki blokkdisszekció a nyaki nyirokcsomók staging-je illetve sebészi terápiája céljából, s e két műtéttípus együttes alkalmazása az intézményi multidiszciplináris tumorboard előzetes jóváhagyása alapján.

Eredmények

Az eddigi irodalomban a legmagasabb arány adjuváns terápia nélkül, a primér kemoradioterápiával azonos rövid távú onkológiai, de annál dokumentáltan jobb funkcionális eredményekkel. Jól szelektált páciensek esetében a betegek túlnyomó többsége eredményesen kezelhető sebészi monomodalitás mellett. Először sikerült kimutatni, hogy a sebészi technika direkt módon hatással van a nyaki disszekció nyirokcsomó-hozamára, amely egy független prognosztikai faktor. Első ajánlás a TORS standardizált szerepére a fej-nyaki tumorok kezelésében, a cTNM-től függő algoritmus és terápiás protokoll kidolgozása révén.

Következtetések

A TORS, valamint a funkcionális és szelektív nyaki blokkdisszekció, rizikó-adaptált adjuváns sugárkezeléssel kiegészítve, képesek együttesen a primer kemoradioterápiával egyenértékű onkológiai, de annál jobb funkcionális eredményeket szolgáltatni a T1-T2 oropharyngeális rákok kezelésében.

9. REFERENCES

- [1] Weinstein GS, O'Malley BW. TransOral robotic surgery (TORS). 2012, San Diego, Plural Publishing.
- [2] Lorincz BB, Laban S, Knecht R. [The development of TORS in Europe]. 2013, HNO; 61:294-299.
- [3] Adelstein DJ, Ridge JA, Brizel DM, Holsinger FC, Haughey BH, O'Sullivan B, Genden EM, Beitler JJ, Weinstein GS, Quon H, Chepeha DB, Ferris RL, Weber RS, Movsas B, Waldron J, Lowe V, Ramsey S, Manola J, Yueh B, Carey TE, Bekelman JE, Konski AA, Moore E, Forastiere A, Schuller DE, Lynn J, Ullmann CD. Transoral resection of pharyngeal cancer: summary of a National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting, November 6-7, 2011, Arlington, Virginia. 2012, Head & Neck; 34:1681-1703.
- [4] Lohia S, Rajapurkar M, Nguyen SA, Sharma AK, Gillespie MB, Day TA. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. 2014, JAMA Otolaryngology - Head & Neck Surgery; 140:331-337.
- [5] Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC. Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes. 2006, The Laryngoscope; 116:2150-2155.
- [6] Lorincz BB, Mockelmann N, Busch CJ, Knecht R. Functional Outcomes, Feasibility and Safety of Resection of Trans Oral Robotic Surgery (Tors): A Single-Institution Series of Thirty-Five Consecutive Tors-Cases for Oropharyngeal Squamous Cell Carcinoma. 2014, Head & Neck (online).
- [7] Hashibe M, Sturgis EM. Epidemiology of oral-cavity and oropharyngeal carcinomas: controlling a tobacco epidemic while a human papillomavirus epidemic emerges. 2013, Otolaryngologic Clinics of North America; 46:507-520.

- [8] Nichols AC, Palma DA, Dhaliwal SS, Tan S, Theuer J, Chow W, Rajakumar C, Um S, Mundi N, Berk S, Zhou R, Basmaji J, Rizzo G, Franklin JH, Fung K, Kwan K, Wehrli B, Salvadori MI, Winkquist E, Ernst S, Kuruvilla S, Read N, Venkatesan V, Todorovic B, Hammond JA, Koropatnick J, Mymryk JS, Yoo J, Barrett JW. The epidemic of human papillomavirus and oropharyngeal cancer in a Canadian population. 2013, *Current Oncology*; 20:212-219.
- [9] Ramqvist T, Dalianis T. Oropharyngeal cancer epidemic and human papillomavirus. 2010, *Emerging Infectious Diseases*; 16:1671-1677.
- [10] Ramqvist T, Dalianis T. An epidemic of oropharyngeal squamous cell carcinoma (OSCC) due to human papillomavirus (HPV) infection and aspects of treatment and prevention. 2011, *Anticancer Research*; 31:1515-1519.
- [11] Bentzen SM, Rosenthal DI, Weymuller EA, Trotti A. Increasing toxicity in nonoperative head and neck cancer treatment: investigations and interventions. 2007, *International Journal of Radiation Oncology, Biology, Physics*; 69:S79-82.
- [12] Maxwell JH, Mehta V, Wang H, Cunningham D, Duvvuri U, Kim S, Johnson J, Ferris RL. Quality of life in head and neck cancer patients: Impact of HPV and primary treatment modality. 2014, *The Laryngoscope*; 124:1592-1597.
- [13] Broglie MA, Soltermann A, Haile SR, Roosli C, Huber GF, Schmid S, Stoeckli SJ. Quality of life of oropharyngeal cancer patients with respect to treatment strategy and p16-positivity. 2013, *The Laryngoscope*; 123:164-170.
- [14] Grant DG, Hinni ML, Salassa JR, Perry WC, Hayden RE, Casler JD. Oropharyngeal cancer: a case for single modality treatment with transoral laser microsurgery. 2009, *Archives of Otolaryngology - Head & Neck Surgery*; 135:1225-1230.
- [15] Haughey BH, Hinni ML, Salassa JR, Hayden RE, Grant DG, Rich JT, Milov S, Lewis JS, Jr., Krishna M. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. 2011, *Head & Neck*; 33:1683-1694.
- [16] Lawson G, Matar N, Remacle M, Jamart J, Bachy V. Transoral robotic surgery for the management of head and neck tumors: learning curve. 2011, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 268:1795-1801.

- [17] Cosmidis A, Rame JP, Dassonville O, Temam S, Massip F, Poissonnet G, Poupart M, Marandas P, De Raucourt D, Groupement d'Etudes des Tumeurs de la Tete et du C. T1-T2 NO oropharyngeal cancers treated with surgery alone. A GETTEC study. 2004, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 261:276-281.
- [18] Weinstein GS, O'Malley BW, Jr., Magnuson JS, Carroll WR, Olsen KD, Daio L, Moore EJ, Holsinger FC. Transoral robotic surgery: a multicenter study to assess feasibility, safety, and surgical margins. 2012, *The Laryngoscope*; 122:1701-1707.
- [19] Lamarre ED, Seth R, Lorenz RR, Esclamado R, Adelstein DJ, Rodriguez CP, Saxton J, Scharpf J. Intended single-modality management of T1 and T2 tonsillar carcinomas: retrospective comparison of radical tonsillectomy vs radiation from a single institution. 2012, *American Journal of Otolaryngology* 2012; 33:98-103.
- [20] Moncrieff M, Sandilla J, Clark J, Clifford A, Shannon K, Gao K, O'Brien C. Outcomes of primary surgical treatment of T1 and T2 carcinomas of the oropharynx. 2009, *The Laryngoscope*; 119:307-311.
- [21] Richmon J, Quon H, Gourin CG. The effect of transoral robotic surgery on short-term outcomes and cost of care after oropharyngeal cancer surgery. 2013, *The Laryngoscope* (online).
- [22] Dziegielewski PT, Teknos TN, Durmus K, Old M, Agrawal A, Kakarala K, Marcinow A, Ozer E. Transoral robotic surgery for oropharyngeal cancer: long-term quality of life and functional outcomes. 2013, *JAMA Otolaryngology - Head & Neck Surgery*; 139:1099-1108.
- [23] Weinstein GS, O'Malley BW, Jr., Snyder W, Hockstein NG. Transoral robotic surgery: supraglottic partial laryngectomy. 2007, *The Annals of Otology, Rhinology, and Laryngology*; 116:19-23.
- [24] Mendelsohn AH, Remacle M, Van Der Vorst S, Bachy V, Lawson G. Outcomes following transoral robotic surgery: supraglottic laryngectomy. 2013, *The Laryngoscope*; 123:208-214.

- [25] Lorincz BB, Busch CJ, Mockelmann N, Knecht R. Feasibility and safety of transoral robotic surgery (TORS) for early hypopharyngeal cancer: a subset analysis of the Hamburg University TORS-trial. 2014, European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies 2014 (online).
- [26] Le Voyer TE, Sigurdson ER, Hanlon AL, Mayer RJ, Macdonald JS, Catalano PJ, Haller DG. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. 2013, Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology; 21:2912-2919.
- [27] Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. 2006, Annals of Surgery; 244:602-610.
- [28] Cianchi F, Palomba A, Boddi V, Messerini L, Pucciani F, Perigli G, Bechi P, Cortesini C. Lymph node recovery from colorectal tumor specimens: recommendation for a minimum number of lymph nodes to be examined. 2002, World Journal of Surgery; 26:384-389.
- [29] Brunocilla E, Pernetti R, Schiavina R, Borghesi M, Vagnoni V, Rocca GC, Borgatti F, Concetti S, Martorana G. The number of nodes removed as well as the template of the dissection is independently correlated to cancer-specific survival after radical cystectomy for muscle-invasive bladder cancer. 2013, International Urology and Nephrology; 45:711-719.
- [30] Herr HW, Bochner BH, Dalbagni G, Donat SM, Reuter VE, Bajorin DF. Impact of the number of lymph nodes retrieved on outcome in patients with muscle invasive bladder cancer. 2002, The Journal of Urology; 167:1295-1298.
- [31] Konety BR, Joslyn SA, O'Donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the Surveillance, Epidemiology and End Results Program data base. 2003, The Journal of Urology; 169:946-950.

- [32] Briganti A, Chun FK, Salonia A, Gallina A, Zanni G, Scattoni V, Valiquette L, Rigatti P, Montorsi F, Karakiewicz PI. Critical assessment of ideal nodal yield at pelvic lymphadenectomy to accurately diagnose prostate cancer nodal metastasis in patients undergoing radical retropubic prostatectomy. 2007, *Urology*; 69:147-151.
- [33] Johnson TV, Hsiao W, Delman KA, Jani AB, Brawley OW, Master VA. Extensive inguinal lymphadenectomy improves overall 5-year survival in penile cancer patients: results from the Surveillance, Epidemiology, and End Results program. 2010, *Cancer*; 116:2960-2966.
- [34] Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Holscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J, DeMeester TR. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. 2008, *Annals of Surgery*; 248:549-556.
- [35] Volpe CM, Driscoll DL, Douglass HO, Jr. Outcome of patients with proximal gastric cancer depends on extent of resection and number of resected lymph nodes. 2000, *Annals of Surgical Oncology*; 7:139-144.
- [36] Weir L, Speers C, D'Yachkova Y, Olivotto IA. Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer. 2002, *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*; 20:1793-1799.
- [37] Jaber JJ, Zender CA, Mehta V, Davis K, Ferris RL, Lavertu P, Rezaee R, Feustel PJ, Johnson JT. A multi-institutional investigation of the prognostic value of lymph nodal yield in advanced stage oral cavity squamous cell carcinoma (OCSCC). 2013, *Head & Neck* (online).
- [38] Pereira JA, Jimeno J, Miquel J, Iglesias M, Munne A, Sancho JJ, Sitges-Serra A. Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. 2005, *Surgery*; 138:1095-1100, discussion 1100-1091.
- [39] Vas Nunes JH, Clark JR, Gao K, Chua E, Campbell P, Niles N, Gargya A, Elliott MS. Prognostic implications of lymph node yield and lymph node ratio in papillary thyroid carcinoma. 2013, *Thyroid: Official Journal of the American Thyroid Association*; 23:811-816.

- [40] Ebrahimi A, Zhang WJ, Gao K, Clark JR. Nodal yield and survival in oral squamous cancer: Defining the standard of care. 2011, *Cancer*; 117:2917-2925.
- [41] Patel SG, Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, Kowalski LP, Ebrahimi A, Clark JR, Cernea CR, Brandao SJ, Kreppel M, Zoller J, Fliss D, Fridman E, Bachar G, Shpitzer T, Bolzoni VA, Patel PR, Jonnalagadda S, Robbins KT, Shah JP, Gil Z. Lymph node density in oral cavity cancer: results of the International Consortium for Outcomes Research. 2013, *British Journal of Cancer*; 109:2087-2095.
- [42] Agrama MT, Reiter D, Cunnane MF, Topham A, Keane WM. Nodal yield in neck dissection and the likelihood of metastases. 2003, *Otolaryngology - Head and Neck Surgery: Official Journal of American Academy of Otolaryngology- Head and Neck Surgery*; 128:185-190.
- [43] Ebrahimi A, Clark JR, Amit M, Yen TC, Liao CT, Kowalski LP, Kreppel M, Cernea CR, Bachar G, Villaret AB, Fliss D, Fridman E, Robbins KT, Shah JP, Patel SG, Gil Z. Minimum Nodal Yield in Oral Squamous Cell Carcinoma: Defining the Standard of Care in a Multicenter International Pooled Validation Study. 2014, *Annals of Surgical Oncology* (online).
- [44] Yu Y, Wang XL, Xu ZG, Li Q. [Prognostic value of the number of lymph nodes retrieved after selective neck dissection in hypopharyngeal squamous carcinoma]. 2013, *Chinese Journal of Otorhinolaryngology Head and Neck Surgery*; 48:148-153.
- [45] Norling R, Therkildsen MH, Bradley PJ, Nielsen MB, von Buchwald C. Nodal yield in selective neck dissection. 2013, *Acta Oto-Laryngologica*; 133:965-971.
- [46] Friedman M, Lim JW, Dickey W, Tanyeri H, Kirshenbaum GL, Phadke DM, Caldarelli D. Quantification of lymph nodes in selective neck dissection. 1999, *The Laryngoscope*; 109:368-370.
- [47] Morton RP, Gray L, Tandon DA, Izzard M, McIvor NP. Efficacy of neck dissection: are surgical volumes important? 2009, *The Laryngoscope*; 119:1147-1152.
- [48] Upile T, Jerjes W, Nouraei SA, Singh S, Clarke P, Rhys-Evans P, Hopper C, Howard D, Wright A, Sudhoff H, Fisher C, Sandison A. How we do it: a method of neck dissection for histopathological analysis. 2007, *BMC Surgery*; 7:21.

- [49] Park YM, Kim WS, Byeon HK, De Virgilio A, Jung JS, Kim SH. Feasibility of transoral robotic hypopharyngectomy for early-stage hypopharyngeal carcinoma. 2010, *Oral Oncology*; 46:597-602.
- [50] Weinstein GS, O'Malley BW, Jr., Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. 2007, *Archives of Otolaryngology - Head & Neck Surgery*; 133:1220-1226.
- [51] Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. 2010, *Archives of Otolaryngology - Head & Neck Surgery*; 136:1079-1085.
- [52] Moore EJ, Olsen KD, Martin EJ. Concurrent neck dissection and transoral robotic surgery. 2011, *The Laryngoscope*; 121:541-544.
- [53] Genden EM, Park R, Smith C, Kotz T. The role of reconstruction for transoral robotic pharyngectomy and concomitant neck dissection. 2011, *Archives of Otolaryngology - Head & Neck Surgery*; 137:151-156.
- [54] Howard BE, Hinni ML, Nagel TH, Chang YH, Cheng MR, Hayden RE. Submandibular gland preservation during concurrent neck dissection and transoral surgery for oropharyngeal squamous cell carcinoma. 2014, *Otolaryngology - Head and Neck Surgery: Official Journal of American Academy of Otolaryngology- Head and Neck Surgery*; 150:587-593.
- [55] Remacle M, Matar N, Lawson G, Bachy V. Laryngeal advanced retractor system: a new retractor for transoral robotic surgery. 2011, *Otolaryngology - Head and Neck Surgery: Official Journal of American Academy of Otolaryngology- Head and Neck Surgery*; 145:694-696.
- [56] Quon H, Cohen MA, Montone KT, Ziober AF, Wang LP, Weinstein GS, O'Malley BW, Jr. Transoral robotic surgery and adjuvant therapy for oropharyngeal carcinomas and the influence of p16 INK4a on treatment outcomes. 2013, *The Laryngoscope*; 123:635-640.
- [57] Quon H, O'Malley BW, Jr., Weinstein GS. Postoperative adjuvant therapy after transoral robotic resection for oropharyngeal carcinomas: rationale and current treatment approach. 2011, *ORL: Journal for Oto-Rhino-Laryngology and its Related Specialties*; 73:121-130.

- [58] Weinstein GS, Quon H, O'Malley BW, Jr., Kim GG, Cohen MA. Selective neck dissection and deintensified postoperative radiation and chemotherapy for oropharyngeal cancer: a subset analysis of the University of Pennsylvania transoral robotic surgery trial. 2010, *The Laryngoscope*; 120:1749-1755.
- [59] Weinstein GS, Quon H, Newman HJ, Chalian JA, Malloy K, Lin A, Desai A, Livolsi VA, Montone KT, Cohen KR, O'Malley BW. Transoral robotic surgery alone for oropharyngeal cancer: an analysis of local control. 2012, *Archives of Otolaryngology- Head & Neck Surgery*; 138:628-634.
- [60] O'Malley BW, Jr., Weinstein GS, Snyder W, Hockstein NG. Transoral robotic surgery (TORS) for base of tongue neoplasms. 2006, *The Laryngoscope*; 116:1465-1472.
- [61] Chi JJ, Mandel JE, Weinstein GS, O'Malley BW, Jr. Anesthetic considerations for transoral robotic surgery. 2010, *Anesthesiology Clinics*; 28:411-422.
- [62] Hockstein NG, Weinstein GS, O'Malley Jr BW. Maintenance of hemostasis in transoral robotic surgery. 2005, *ORL: Journal for Oto-Rhino-Laryngology and its Related Specialties*; 67:220-224.
- [63] Hockstein NG, O'Malley BW, Jr., Weinstein GS. Assessment of intraoperative safety in transoral robotic surgery. 2006, *The Laryngoscope*; 116:165-168.
- [64] Lawson G, Mendelsohn AH, Van Der Vorst S, Bachy V, Remacle M. Transoral robotic surgery total laryngectomy. 2013, *The Laryngoscope*; 123:193-196.
- [65] Bhattacharyya N. The effects of more conservative neck dissections and radiotherapy on nodal yields from the neck. 1998, *Archives of Otolaryngology - Head & Neck Surgery*; 124:412-416.
- [66] Gavilán J. Functional and selective neck dissection. 2002, New York, Thieme; pp. xiv, 161 p.
- [67] Ferlito A, Gavilan J, Buckley JG, Shaha AR, Miodonski AJ, Rinaldo A. Functional neck dissection: Fact and fiction. 2011, *Head & Neck*; 23:804-808.
- [68] Kerawala CJ, Bisase B, Hopper A. Is total nodal yield in neck dissections influenced by the method of specimen presentation to the pathologist? 2009, *The British Journal of Oral & Maxillofacial Surgery*; 47:360-362.

- [69] Ferlito A, Rinaldo A, Silver CE, Shah JP, Suarez C, Medina JE, Kowalski LP, Johnson JT, Strome M, Rodrigo JP, Werner JA, Takes RP, Towpik E, Robbins KT, Leemans CR, Herranz J, Gavilan J, Shaha AR, Wei WI. Neck dissection: then and now. 2006, *Auris, Nasus, Larynx*; 33:365-374.
- [70] Gavilan J, Gavilan C, Herranz J. Functional neck dissection: three decades of controversy. 1992, *The Annals of Otology, Rhinology, and Laryngology*; 101:339-341.
- [71] Gavilan C, Gavilan J. Five-year results of functional neck dissection for cancer of the larynx. 1989, *Archives of Otolaryngology - Head & Neck Surgery*; 115:1193-1196.
- [72] Patel RS, Clark JR, Gao K, O'Brien CJ. Effectiveness of selective neck dissection in the treatment of the clinically positive neck. 2008, *Head & Neck*; 30:1231-1236.
- [73] Url C, Schartinger VH, Riechelmann H, Gluckert R, Maier H, Trumpp M, Widmann G. Radiological detection of extracapsular spread in head and neck squamous cell carcinoma (HNSCC) cervical metastases. 2013, *European Journal of Radiology*; 82:1783-1787.
- [74] Zoumalan RA, Kleinberger AJ, Morris LG, Ranade A, Yee H, DeLacure MD, Myssiorek D. Lymph node central necrosis on computed tomography as predictor of extracapsular spread in metastatic head and neck squamous cell carcinoma: pilot study. 2010, *The Journal of Laryngology and Otology*; 124:1284-1288.
- [75] Cozzi L, Fogliata A, Bolsi A, Nicolini G, Bernier J. Three-dimensional conformal vs. intensity-modulated radiotherapy in head-and-neck cancer patients: comparative analysis of dosimetric and technical parameters. 2004, *International Journal of Radiation Oncology, Biology, Physics*; 58:617-624.
- [76] Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, Morrison W, Glisson B, Trotti A, Ridge JA, Thorstad W, Wagner H, Ensley JF, Cooper JS. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. 2013, *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*; 31:845-852.

- [77] Nguyen NP, Moltz CC, Frank C, Vos P, Smith HJ, Karlsson U, Dutta S, Midyett FA, Barloon J, Sallah S. Dysphagia following chemoradiation for locally advanced head and neck cancer. 2004, *Annals of Oncology: Official Journal of the European Society for Medical Oncology (ESMO)*; 15:383-388.
- [78] Iseli TA, Kulbersh BD, Iseli CE, Carroll WR, Rosenthal EL, Magnuson JS. Functional outcomes after transoral robotic surgery for head and neck cancer. 2009, *Otolaryngology - Head and Neck Surgery: Official Journal of American Academy of Otolaryngology- Head and Neck Surgery*; 141:166-171.
- [79] More YI, Tsue TT, Girod DA, Harbison J, Sykes KJ, Williams C, Shnayder Y. Functional swallowing outcomes following transoral robotic surgery vs primary chemoradiotherapy in patients with advanced-stage oropharynx and supraglottis cancers. 2013, *JAMA Otolaryngology - Head & Neck Surgery*; 139:43-48.
- [80] Park YM, Kim WS, De Virgilio A, Lee SY, Seol JH, Kim SH. Transoral robotic surgery for hypopharyngeal squamous cell carcinoma: 3-year oncologic and functional analysis. 2012, *Oral Oncology*; 48:560-566.
- [81] Yim EK, Park JS. The role of HPV E6 and E7 oncoproteins in HPV-associated cervical carcinogenesis. 2005, *Cancer Research and Treatment: Official Journal of the Korean Cancer Association*; 37:319-324.
- [82] Jordan RC, Lingen MW, Perez-Ordóñez B, He X, Pickard R, Koluder M, Jiang B, Wakely P, Xiao W, Gillison ML. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. 2012, *The American Journal of Surgical Pathology*; 36:945-954.
- [83] Barten M, Ostwald C, Milde-Langosch K, Müller P, Wukasz Y, Loning T. HPV DNA and p53 alterations in oropharyngeal carcinomas. 1995, *Virchows Archiv: an International Journal of Pathology*; 427:153-157.
- [84] Kumar B, Cordell KG, Lee JS, Worden FP, Prince ME, Tran HH, Wolf GT, Urban SG, Chepeha DB, Teknos TN, Eisbruch A, Tsien CI, Taylor JM, D'Silva NJ, Yang K, Kurnit DM, Bauer JA, Bradford CR, Carey TE. EGFR, p16, HPV Titer, Bcl-xL and p53, sex, and smoking as indicators of response to therapy and survival in oropharyngeal cancer. 2008, *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*; 26:3128-3137.

- [85] Worsham MJ, Stephen JK, Chen KM, Mahan M, Schweitzer V, Havard S, Divine G. Improved survival with HPV among African Americans with oropharyngeal cancer. 2013, *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*; 19:2486-2492.
- [86] Ampil F, Chaudhery S, Devarakonda S, Mills G. Extended survival after chemotherapy and conservative radiotherapy for HPV-16 positive stage IVB oropharyngeal carcinoma. 2013, *Acta Oncologica*; 52:1236-1237.
- [87] Lill C, Kornek G, Bachtary B, Selzer E, Schopper C, Mittlboeck M, Burian M, Wrba F, Thurnher D. Survival of patients with HPV-positive oropharyngeal cancer after radiochemotherapy is significantly enhanced. 2011, *Wiener Klinische Wochenschrift*; 123:215-221.
- [88] Genden EM. The role for surgical management of HPV-related oropharyngeal carcinoma. 2012, *Head and Neck Pathology*; 6 Suppl 1:S98-103.
- [89] Leonhardt FD, Quon H, Abrahao M, O'Malley BW, Jr., Weinstein GS. Transoral robotic surgery for oropharyngeal carcinoma and its impact on patient-reported quality of life and function. 2012, *Head & Neck*; 34:146-154.
- [90] Genden EM, O'Malley BW, Jr., Weinstein GS, Stucken CL, Selber JC, Rinaldo A, Hockstein NG, Ozer E, Mallet Y, Satava RM, Moore EJ, Silver CE, Ferlito A. Transoral robotic surgery: role in the management of upper aerodigestive tract tumors. 2012, *Head & Neck*; 34:886-893.
- [91] Sinclair CF, McCulloch NL, Carroll WR, Rosenthal EL, Desmond RA, Magnuson JS. Patient-perceived and objective functional outcomes following transoral robotic surgery for early oropharyngeal carcinoma. 2011, *Archives of Otolaryngology - Head & Neck Surgery*; 137:1112-1116.
- [92] Hans S, Jouffroy T, Veivers D, Hoffman C, Girod A, Badoual C, Rodriguez J, Brasnu D. Transoral robotic-assisted free flap reconstruction after radiation therapy in hypopharyngeal carcinoma: report of two cases. 2013, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 270:2359-2364.
- [93] Richmon JD, Quon H, Gourin CG. The effect of transoral robotic surgery on short-term outcomes and cost of care after oropharyngeal cancer surgery. 2014, *The Laryngoscope*; 124:165-171.

- [94] Kofler B, Laban S, Busch CJ, Lorincz B, Knecht R. New treatment strategies for HPV-positive head and neck cancer. 2014, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 271:1861-1867.
- [95] Cohen MA, Weinstein GS, O'Malley BW, Jr., Feldman M, Quon H. Transoral robotic surgery and human papillomavirus status: Oncologic results. 2011, *Head & Neck*; 33:573-580.
- [96] Fischer CA, Zlobec I, Green E, Probst S, Storck C, Lugli A, Tornillo L, Wolfensberger M, Terracciano LM. Is the improved prognosis of p16 positive oropharyngeal squamous cell carcinoma dependent of the treatment modality? 2010, *International Journal of Cancer*; 126:1256-1262.
- [97] Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, Oggionni M, Rossini C, Cantu G, Squadrelli M, Quattrone P, Locati LD, Bergamini C, Olmi P, Pierotti MA, Pilotti S. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. 2006, *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*; 24:5630-5636.
- [98] Hong AM, Dobbins TA, Lee CS, Jones D, Harnett GB, Armstrong BK, Clark JR, Milross CG, Kim J, O'Brien CJ, Rose BR. Human papillomavirus predicts outcome in oropharyngeal cancer in patients treated primarily with surgery or radiation therapy. 2010, *British Journal of Cancer*; 103:1510-1517.
- [99] Salazar CR, Smith RV, Garg MK, Haigentz M, Jr., Schiff BA, Kawachi N, Anayannis N, Belbin TJ, Prystowsky MB, Burk RD, Schlecht NF. Human Papillomavirus-Associated Head and Neck Squamous Cell Carcinoma Survival: A Comparison by Tumor Site and Initial Treatment. 2013, *Head and Neck Pathology* (online).
- [100] Lassaletta L, Garcia-Pallares M, Morera E, Salinas S, Bernaldez R, Patron M, Gavilan J. Functional neck dissection for the clinically negative neck: effectiveness and controversies. 2002, *The Annals of Otology, Rhinology, and Laryngology*; 111:169-173.

- [101] Nichols AC, Yoo J, Hammond JA, Fung K, Winkquist E, Read N, Venkatesan V, MacNeil SD, Ernst DS, Kuruvilla S, Chen J, Corsten M, Odell M, Eapen L, Theurer J, Doyle PC, Wehrli B, Kwan K, Palma DA. Early-stage squamous cell carcinoma of the oropharynx: radiotherapy vs. trans-oral robotic surgery (ORATOR) -study protocol for a randomized phase II trial. 2013, BMC Cancer; 13:133.
- [102] Kunzel J, Psychogios G, Mantsopoulos K, Grundtner P, Waldfahrer F, Iro H. Lymph node ratio as a predictor of outcome in patients with oropharyngeal cancer. 2013, European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (online).
- [103] Quon H, Richmon JD. Treatment deintensification strategies for HPV-associated head and neck carcinomas. 2012, Otolaryngologic Clinics of North America; 45:845-861.

10. PUBLICATIONS

10.1. Related to the Ph.D. Thesis

1. Lorincz BB, Mockelmann N, Busch CJ, Knecht R. Functional outcomes, feasibility, and safety of resection of transoral robotic surgery: Single-institution series of 35 consecutive cases of transoral robotic surgery for oropharyngeal squamous cell carcinoma. 2014, Head & Neck (online).
2. Lorincz BB, Busch CJ, Mockelmann N, Knecht R. Feasibility and safety of transoral robotic surgery (TORS) for early hypopharyngeal cancer: a subset analysis of the Hamburg University TORS-trial. 2014, European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (online).
3. Lorincz BB, Knecht R. [Transoral robotic total laryngectomy and neck dissection: the concept of robotic combo surgery]. 2013, Laryngo-Rhino-Otologie; 92:585-588.
4. Lorincz BB, Laban S, Knecht R. [The development of TORS in Europe]. 2013, HNO; 61:294-299.

10.2. Other Publications

5. Lorincz BB, Mockelmann N, Knecht R. Single-incision transaxillary robotic total thyroidectomy for Graves' disease: improved feasibility and safety with novel robotic instrumentation. 2014, European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (online).
6. Kofler B, Laban S, Busch CJ, Lorincz B, Knecht R. New treatment strategies for HPV-positive head and neck cancer. 2014, European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies; 271:1861-1867.

7. Jowett N, Wöllmer W, Reimer R, Zustin J, Schumacher U, Wiseman PW, Mlynarek AM, Böttcher A, Dalchow CV, Lörincz BB, Knecht R, Miller RJ. Bone ablation without thermal or acoustic mechanical injury via a novel picosecond infrared laser (PIRL). 2014, *Otolaryngology - Head and Neck Surgery: Official Journal of American Academy of Otolaryngology- Head and Neck Surgery*; 150:385-393.
8. Lorincz BB, Mandapathil M. [Robot-assisted transoral tumor surgery possible]. 2013, *Laryngo-Rhino-Otologie*; 92:642-643.
9. Bottcher A, Knecht R, Busch CJ, Lörincz BB, Dalchow CV. [Hereditary sensorineural hearing impairment and macrothrombocytopenia: a rare MYH9 gene mutation]. 2013, *HNO*; 61:159-160, 162-155.
10. Ebrahimi A, Clark JR, Lorincz BB, Milross CG, Veness MJ. Metastatic head and neck cutaneous squamous cell carcinoma: defining a low-risk patient. 2012, *Head & Neck*; 34:365-370.
11. Peters P, Stark P, Essig G Jr, Lorincz B, Bowman J, Tran K, Coman S. Lingual thyroid: an unusual and surgically curable cause of sleep apnoea in a male. 2010, *Sleep & Breathing = Schlaf & Atmung*; 14:377-380.
12. Lorincz BB, Kalman E, Gerlinger I. KTP-532 laser-assisted microvascular anastomosis (experimental animal study). 2007, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 264:823-828.
13. Lorincz BB, Lichtenberger G, Bihari A, Falvai J. Therapy of periprosthetic leakage with tissue augmentation using Bioplastique around the implanted voice prosthesis. 2005, *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies*; 262:32-34.

11. ACKNOWLEDGEMENTS

Katalin Hutter, Oliver Lörincz, György Lörincz Jr., Katalin Lörincz, György Lörincz Sr., Aranka Török, Borbála Lörincz, Hilda Kobia, Ferenc Gallyas, Imre Gerlinger, +György Lichtenberger, Károly Polus, Jan Olofsson, William Coman, Chris Perry, +Frank Szallasi, Chris O'Brien, Jonathan Clark, Kerwin Shannon, Ardalan Ebrahimi, Suren Krishnan, Theo Gregor, Rainald Knecht, Nikolaus Möckelmann, Chia-Jung Busch, Nathan Jowett, Geza Jako, György Weber, Georges Lawson, Marc Remacle, Gregory Weinstein, Neil Tolley, Asit Arora, Kyung Tae, Micaela Piccoli, Tiziana Bonciani, Sabine Pohlmann, Javier Gavilan and K. Thomas Robbins.