

# Patient Benefit and Quality of Life after Robot-Assisted Head and Neck Surgery



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## ABSTRACT

Robotic systems for head and neck surgery are at different stages of technical development and clinical application. Currently, robotic systems are predominantly used for transoral surgery of the pharynx and larynx. Robotic surgery of the neck, the thyroid, and the middle and inner ear is much less common; however, some oncological and functional outcomes have been reported. This article provides an overview of the current state of robot-assisted head and neck surgery with a special emphasis on patient benefit and postoperative quality of life (QoL). The focus is placed on the role of transoral robotic surgery (TORS) for the resection of oropharyngeal carcinomas. For this application, reported long-term outcomes show functional post-operative advantages for selected oropharyngeal cancer patients after TORS compared to open surgery and primary radiotherapy. Since TORS also plays a significant role in the context of potential therapy de-escalation for HPV-positive oropharyngeal cancer patients, ongoing trials are presented. Regarding the evaluation of the therapeutic benefit and the QoL of cancer patients, special attention has to be paid to the large degree of variability of individual patients' preferences. Influencing factors and tools for a detailed assessment of QoL parameters are therefore detailed at the beginning of this article. Notably, while some robotic systems for ear and skull base surgery are being developed in Europe, TORS systems are mainly used in North America and Asia. In Europe and Germany in particular, transoral laser microsurgery (TLM) is a well-established technology for transoral tumor resection. Future trials comparing TORS and TLM with detailed investigation of QoL parameters are therefore warranted and might contribute to identifying suitable fields for the application of the different techniques.

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## 1 Introduction

Randomized controlled trials are routinely performed prior to clinically establishing new non-surgical diagnostic and therapeutic procedures such as instruments used in radiology or new medications. Complex and innovative surgical procedures, however, are typically first tested in specifically selected patients so that the usual criteria of evidence-based medicine cannot be met from the outset. Discussions are ongoing to which extent and at which time point new surgical procedures have to be evaluated before they can be accepted as standard therapy [1]. But there is a broad consensus that a thorough evaluation of their benefit compared to alternative procedures and their long-term outcome after application is essential for the patients. Robotic systems for head and neck surgery have been in use for nearly two decades allowing for a review of long-term therapy outcomes. In the following article, different robotic systems and applications for robotic head and neck surgery are reviewed with an emphasis on the potential patient benefit.

The specific definitions of the terms “patient benefit” and “quality of life” in the context of robotic head and neck surgery are variable and depend on the anatomic region of application as well as technical specifications of the robotic system. Technologically, the spectrum of robotic systems ranges from simple support systems which are guided by the surgeon’s own hands to complex tele-operated systems with hands-off effector tools or even completely autonomous systems which perform procedures independently after specific programming. A first-generation robotic system was used over 30 years ago by American neurosurgeons who biopsied brain tumors with a modified industrial robot with manipulators of several degrees of freedom [2]. The actual biopsy was acquired manually but the precision was increased by positioning the biopsy needle with the so-called PUMA (programmable universal machine for assembly). Patients were expected to benefit from more precise tissue specimens and reduced iatrogenic trauma. Today’s most-used robotic system in head and neck surgery is much more complex. The tele-operated DaVinci system (Intuitive Surgical, Sunnyvale, USA) was developed in the early 2000s and is well-established for clinical use at this point. Besides potentially increasing surgical precision, the tele-operated effector tools and camera systems

allow for a transoral approach to the pharynx and larynx, hereby avoiding a more invasive external access. First results of the clinical application of transoral robotic surgery (TORS) with the da Vinci system were published in 2006 [3–7], and showed the system’s potential to completely resect tumors of the base of tongue. Compared to alternative therapeutic options, patients benefited from complete tumor resection via a less traumatic approach, hereby preserving postoperative function. Accordingly, TORS is the main application of robotic technology in the head and neck and is routinely used for the resection of pharyngeal and some laryngeal carcinomas. Here, the key parameters for the definition of patient benefit and quality of life are related to the oncological outcome and the preservation of specific functions such as swallowing and speaking. However, despite numerous technological developments such as improved camera technology or space-saving effector tools, to date robot-assisted surgeries have only been established as standard therapy for selected cases and in certain regions of the world. In the US in particular, these include the aforementioned transoral robotic resection of oropharyngeal tumors. The increasing incidence of oropharyngeal squamous cell carcinomas (OPSCC) associated with the human papilloma virus (HPV) is clearly the driver of a paradigm shift from open surgical approaches or primary radiotherapy towards potentially less invasive TORS [8, 9]. HPV-associated OPSCC show a much-improved response to both surgical and non-surgical therapy compared to non-HPV-associated OPSCC. Improved survival in mostly younger and overall healthier patients has put forward quality of life considerations [10, 11]. Consequently, innovative surgical technologies which could potentially improve patients’ quality of life such as TORS were promoted. Notably, there are pronounced regional differences regarding the use of TORS. While TORS is well-established in the US for OPSCC surgery, data from Germany and Europe is scarce. In Germany in particular, transoral laser microsurgery (TLM) has been well-established since the 1980ies it is commonly used as an alternative to open surgery for the transoral resection of pharyngeal and laryngeal carcinomas [12]. In the US, TLM was never as well-established as alternative to open surgery or primary radiotherapy and in many centers, TORS was the first transoral surgical technology to be adopted. Accordingly, long-term study results from the US have been published regarding the oncological benefit and functional quality of life after TORS; however, any direct comparison with TLM is difficult because the techniques are rarely applied at the same institution.

The following article will attempt to provide an overview regarding the potential patient benefit and post-operative quality of life after robotic surgery for OPSCC as well as other areas of head and neck surgery. This includes the use of robotic systems for transoral tumor resection in the larynx and hypopharynx where the DaVinci system and the FLEX system (Medrobotics Corporation, Raynham, USA) are routinely used. In Asia, the DaVinci robot is also used for neck surgery, thyroid surgery, and salivary gland surgery via external approaches. First clinical results regarding the application of alternative robotic systems for ear surgery have been reported by French and Swiss groups. Depending on the field of application, the definitions of patient benefit and quality of life may differ; in non-oncological surgery, aspects of organ-specific function as well as aesthetics play a dominant role.

Nevertheless, the resection of malignant tumors is currently the main application of robotics in head and neck surgery. Therefore, at the outset of the article, the definitions and methods of assessment of patient benefit and quality of life in the context of oncological diseases of the head and neck are presented, followed by a short overview of the current state of robotic technology. It should be noted that any definition of therapy benefit depends on perspective; individual patients may have different priorities than other affected individuals or than their treating therapists, depending on their age and life situation. Individually defined quality of life considerations therefore contribute to the individual patient's therapeutic benefit and may influence therapy decisions. Knowledge about the preferences of specific patient groups is therefore desirable for both pre-therapeutic counseling and post-therapeutic assessment. Assessing the respective quality of life parameters is challenging and various tools have been developed in recent years, which will also be presented at the beginning of the article.

## 2 Head and neck cancer patients' therapy benefit and quality of life

### 2.1 Definition and influencing factors

The value of a medical therapy is usually defined by the parameters "efficacy" and "therapy cost" over the total duration of therapy [13]. However, in the therapy of malignant diseases, the "efficacy", i. e. the therapy response, is often dependent on the intensity and invasiveness of the therapy, which in turn may negatively influence post-operative quality of life. The assessment of the final therapeutic outcome for the patient, i. e., the "patient benefit," may therefore differ substantially between individual patients. The same can be said for therapists. Discrepancies between the therapy goals of head and neck cancer patients and treating physicians were impressively demonstrated in the 1980s: While treating physicians almost consistently preferred the therapy with the greatest chance of cure, McNeil and colleagues demonstrated that for some patients with laryngeal cancer, preserving speech function was more important than maximizing their potential life quantity, i. e., their statistically remaining life expectancy [14]. Up to 20% of patients interviewed in the study indicated that they would prefer organ-preserving nonsurgical therapy to total laryngectomy despite up to a 30% lower chance of permanent cure. More recent data confirmed these data and showed that a certain proportion of patients affected by laryngeal carcinoma would be willing to accept significant statistical losses in statistical survival for organ preservation and thus preservation of natural speech [15–17]. This is an extreme example, as total laryngectomy has a high impact on patients' life circumstances; usually, cure and survival are the highest priorities for head and neck cancer patients [18]. Apart from the fundamental question of quality of life vs. quantity of life however, quality of life parameters can vary widely depending on the disease or individual patient characteristics. They have been studied in detail in recent years. For example, patient age influences the weighting of qualitative and quantitative endpoints, as do socioeconomic differences [18].

The interpretation of respective trials on QoL preferences of cancer patients is highly complex because these may also change intra-individually over the course of the disease. Among other things, the timing of the patient interview in relation to the therapy, the individual therapy response and technological developments associated with a changed spectrum of side effects were identified as influencing factors on the respective preferences. The term "decision regret" was coined in the English-language literature to describe the shift in patient preferences after therapy completion [19, 20]. It is now well established that patients' preferences can change after therapy compared to their pre-therapeutic assessment, because new life situations arise, or therapeutic side effects were previously assessed incorrectly. Recent studies on patients with oropharyngeal carcinoma show that changes affecting patients' prognosis and thus the average survival time after therapy influence the weighting of quality of life preferences. For example, patients with human papillomavirus (HPV)-associated oropharyngeal carcinomas have a significantly better chance of cure than patients with HPV-negative carcinomas and therefore a longer average post-therapy survival [10, 21].

Despite presenting with comparable symptoms, the weightings in the definition of therapy benefit in patients with HPV-positive oropharyngeal carcinoma patients can differ significantly from patients with HPV-negative tumors. In particular, the long-term therapy side effects which influence quality of life parameters such as swallowing ability and speech in patients with a significantly higher post-therapeutic life expectancy lead to up to 60% of patients with HPV-associated oropharyngeal carcinomas stating that they permanently suffer from severe limitations, which were not adequately considered in the therapy decision [22]. In contrast, HPV-negative patients, whose disease is associated with a significantly worse prognosis, are subjectively less burdened by corresponding quality of life limitations after successful therapy. Technical developments in surgical and non-surgical therapy can also significantly influence quality of life parameters and thus patient preferences. In recent decades, the widespread introduction of intensity-modulated radiation therapy (IMRT) has played an important role in radiotherapy. Several trials show a post-therapeutic clinical benefit for head and neck cancer patients after IMRT compared to conventional radiotherapy. The reduction of the radiation dose in the area of the salivary glands decisively influences the side effects of the treatment [23–25].

One quality of life parameter considered very important by patients, namely post-therapeutic dry mouth and associated limitations in swallowing, is significantly less pronounced after IMRT, thus rendering older study results on conventional radiotherapy obsolete. A similar development could be observed in the field of surgical therapy options: The establishment of transoral robotic-assisted surgery is shifting treatment preferences for patients with head and neck tumors, especially in regions where no alternative transoral therapy procedures were previously available. Study results from recent years show that TORS can achieve better functional results in patients with oropharyngeal carcinoma compared to open surgical therapy, especially with regard to the parameters of swallowing ability and speech preservation, which are important for quality of life. [26, 27]. Here, too, older studies comparing quality of life parameters after open surgical therapy versus non-sur-

gical therapy should at least be questioned. Since healthy relatives, e. g. spouses and children, are often included in the treatment planning of head and neck tumor patients, their assessments may influence the choice of therapy. This is relevant from the therapist's point of view. Several studies compared not only the preferences of different patient groups, but also differences in assessment between patients and their healthy relatives. Interestingly, young healthy respondents assessed the late effects of therapy as significantly more burdensome than the affected head and neck tumor patients related to them [28]. Higher congruence was found in the weighting of the preferences between cancer patients and their life partners [20].

## 2.2 Most important quality of life parameters

With the exception of some patients with laryngeal carcinoma, who place the highest priority on preserving their natural speech, studies of nearly all other head and neck tumor entities show that the parameters related to cure and survival are consistently given the highest priority [29–32]. Although this finding may seem obvious, it should nevertheless be emphasized as it is the basic prerequisite for any new therapy or modification – a reduction in morbidity is only valuable if the chances of cure or survival are not negatively affected. A certain proportion of patients may be willing to accept small losses in terms of their statistical chances of cure to reduce the side effects of their therapy. According to studies, however, on average, the range of accepted reduction in the chance of healing in favor of improved post-operative functional preservation is around 5% [33]. Secondary quality of life factors show a much more heterogeneous distribution of weighting, depending on both patient characteristics and tumor location. After cure and survival, freedom from pain comes first for many patients [20, 34]. Further, lower-ranking preferences depend on tumor location: patients with oropharyngeal and oral cavity carcinomas tend to view swallowing and chewing as post-therapy quality of life factors with high priority. In contrast, preservation or rehabilitation of speech function is a priority for patients with laryngeal carcinomas [35, 36]. Interestingly, in a German study by Tschiesner and co-authors, after survival and cure, patients with a tumor in the head and neck region assigned the highest priority to the coverage of direct and indirect therapy costs [37]. This factor is rarely mentioned in international studies and is surprising in view of the cost coverage provisions in the German healthcare system. The authors of the study speculate that the information provided by patients primarily relates to indirect costs, which result, for example, from a potential inability to return to their job after therapy. Extensive studies have shown that patients are sometimes unable to continue their previous work after tumor diseases and thus suffer significant losses of income [38]. Overall, apart from the key parameters cure and survival, individual patient profiles with regard to the weighting of the quality of life parameters are heterogeneous and depend on multiple factors.

## 2.3 Assessment of quality of life parameters

By definition, "quality of life" summarizes aspects of a person's physical, mental and social health [39]. In a medical context, quality of life parameters are usually queried in relation to the disease or the corresponding therapy, especially when it comes to evaluating pa-

tients' therapy benefit. For the assessment of the quality of life of patients with head and neck tumors at different points over the course of the disease, several methods have been established, namely the evaluation of clinical indicators, the assessment by means of questionnaires or special clinical examinations. As described above, the individual definition of "quality of life" in patients with head and neck tumors is very heterogeneous. However, it is well documented that oropharyngeal cancer patients attach outstanding importance to their post-therapeutic swallowing ability after the primary therapy goals of survival and cure [40]. Since transoral resection of oropharyngeal carcinomas is currently the main field of application of robotic surgery in the head and neck region, clinical indicators, questionnaires and clinical examination methods that can be used to record the quality of life and the swallowing ability of these patients are summarized below. Clinical indicators, unlike questionnaires or specific clinical examinations, are rather crude parameters for recording functional limitations, but are suitable for retrospective evaluation of therapeutic procedures. In patients with oropharyngeal carcinoma, these include the need for and duration of gastric tube or percutaneous endoscopic gastrostomy (PEG) tube placement. As a rule, a PEG tube is used primarily for patients for whom a post-operative oral diet is not possible. In addition to the purely functional restriction, a PEG tube has been shown to have a serious impact on the overall quality of life of tumor patients, since life with family members is strongly affected [41–43]. In addition, there are undesirable side effects, such as the potential long-term negative impact on swallowing ability due to muscular and neurological changes, which make a subsequent switch to oral nutrition much more difficult [44]. A purely prophylactic post-operative PEG tube placement must therefore be questioned. In some studies on patients with oropharyngeal carcinoma, the change in body weight of the patients over time is also used as an indicator for assessing post-operative food intake. It is measured as a percentage of the patients' initial weight and is divided into grades [45]. The advantage of this method is the recording of the total food intake independent of the route of delivery, but it is only meaningful in combination with other functional parameters for the assessment of swallowing ability. The necessity and duration of peri-operative tracheostomy in the context of transoral tumor surgery is regularly recorded in corresponding studies. Patients find the permanent fitting of a tracheostomy tube to be extremely stressful, as both swallowing and speaking ability are negatively affected. However, in contrast to the initial TORS patients with oropharyngeal carcinoma where tracheostomy was regularly performed, the current temporary and permanent tracheostomy rate is very low [46].

Several tools are available for the standardized and detailed assessment of swallowing. For example, the *Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)* or the *Functional Outcomes Swallowing Scale (FOSS)* are applied and recorded by the therapists. The *Eating Assessment Tool (EAT-10)*, the *MD Anderson Dysphagia Inventory (MDADI)*, the *Functional Assessment of Cancer Therapy (FACT)*, or the *Sydney Swallow Questionnaire (SSQ)* are based on patient-reported data. The two latter mentioned tools are similar to the MDADI with regard to the information provided [47]. ▶ **Table 1** provides an overview of the acquisition tools mentioned, FACT and SSQ are not listed due to their redundancy to MDADI.

► **Table 1** Overview of standardized tools to assess the swallowing capacity of cancer patients. The two first mentioned instruments are based on an estimation by the therapist, the other two questionnaires are filled out by the patients.

Tool	Assessment	Details
<i>Performance Status Scale for Head and Neck Cancer Patients</i> (PSS-HN) [48]	Therapist-based	<ul style="list-style-type: none"> <li>Assesses nutrition habits on a scale of 0–100</li> <li>Allows an estimation of the patients' ability to take in food of different consistencies</li> </ul>
<i>Functional Outcomes Swallowing Scale</i> (FOSS) [49]	Therapist-based	<ul style="list-style-type: none"> <li>Scale of 6 grades, 0 corresponds to normal function, 5 means no oral food intake</li> <li>Rapid assessment in simple categories</li> </ul>
<i>Eating Assessment Tool</i> (EAT-10) [50]	Patient-based	<ul style="list-style-type: none"> <li>10 items to assess the swallowing ability</li> <li>Validated for the correlation with the risk of aspiration during swallowing of head and neck cancer patients after therapy [51–52]</li> </ul>
<i>MD Anderson Dysphagia Inventory</i> (MDADI) [53]	Patient-based	<ul style="list-style-type: none"> <li>20 items regarding 4 swallowing-associated QoL areas (global, emotional, functional, physical)</li> <li>Higher scores correspond to better function and higher QoL</li> <li>Good correlation with duration of tube feeding and also with tumor stage and complications [54]</li> </ul>

In relation to the individual patient, functional diagnostics play a role in addition to the aforementioned standardized questionnaires. The flexible endoscopic evaluation of swallowing (FEES) and the barium swallow examination allow conclusions to be drawn about the cause of the functional restriction. FEES allows direct endoscopic inspection of the swallowing process in the pharynx. After surgical resection, a detailed endoscopic wound inspection is also possible (► **Fig. 1**). In contrast, barium swallow examination (► **Fig. 2**) shows the flow of the bolus in relation to the surrounding anatomy and may therefore be more sensitive for the detection of aspiration events [55]. For the barium swallow examination, the results can be quantified using the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) method to make them comparable. [56]. A study of patients with TORS-treated oropharyngeal carcinoma patients showed that post-operative limitations could be reliably detected over time and that a DIGEST score greater than or equal to 2 reliably reflects clinically apparent moderate to severe dysphagia [57].

Tools that allow for a comprehensive analysis of the overall quality of life of tumor patients have also been established. There is a large number of available questionnaires, but the most commonly used are the QLQ-C30 and QLQ-H&N35 of the European Organization for Research and Treatment of Cancer (EORTC), the University of Washington Quality of Life (UW-QOL) and the MD Anderson Symptom

Inventory – Head and Neck Module (MDASI-HN) [58]. ► **Table 2** provides an overview of the three mentioned questionnaires.

The listed questionnaires and clinical examination tools offer a variety of ways to assess post-operative function and quality of life in patients after therapy for OPSCC and other head and neck tumors. Nevertheless, in addition to cure and survival data, many of the studies reviewed in the following chapters primarily evaluate clinical parameters, such as the duration of gastrostomy tube or tracheostomy tube use. For future studies, a consistent application of the available tools would be desirable to evaluate patient benefit and quality of life in comparison of different therapies in more detail.

### 3 Robot-assisted surgery of the head and neck: state of the art

This review article is focused on the evaluation of robotic-assisted surgery in the head and neck with regard to patient benefit and quality of life and does not have the main objective of highlighting technical or economic aspects of robotic technology. Extensive German-language publications from the past years have been published [65, 66]. Nevertheless, a brief look at the current state of the art is indispensable, as robotic systems for head and neck surgery are subject to constant technological development. This may affect the surgical fields of application and therapy results and thus impact patient-related aspects such as healing or survival and secondary quality of life parameters.

#### 3.1 DaVinci and FLEX system

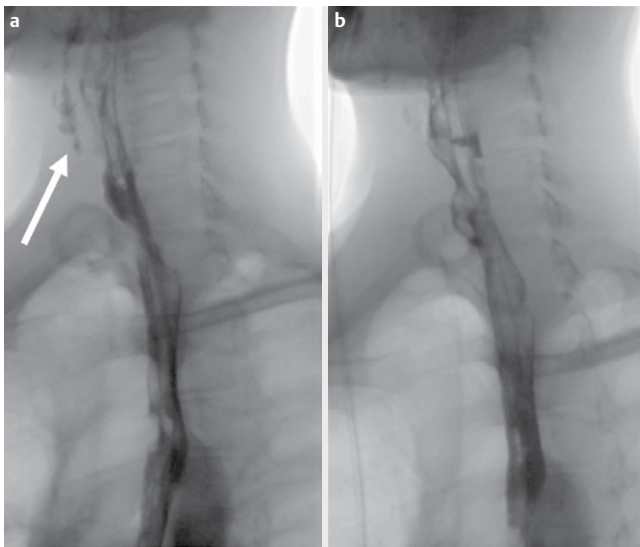
In head and neck surgery, the da Vinci system from Intuitive Surgical (Sunnyvale, USA) is used most frequently and is commonly used at specialized centers in the US for the transoral resection of oropharyngeal carcinomas. While the main areas of application of the system continue to be in abdominal surgery, gynecologic and urologic surgery [67, 68], technical developments have expanded its range of application to the pharynx and larynx. The system consists of a console, from which the surgeon remotely controls the robotic arms, and the actual robot, which consists of three instrument arms and a camera arm. The da Vinci system has gone through various generations; currently, the so-called X-generation is being marketed. In addition, a single-port system (► **Fig. 3a**) has been developed, in which three instruments and the endoscope are inserted through a single 2.5 cm diameter working channel. Other key technological innovations in recent years have included the positioning of the robotic arms above the patient, whereas in previous versions they were positioned beside the patient, and the integration of 3D visualization. For transoral head and neck surgery, the development of the single-port system is promising, as this facilitates the application in the limited anatomical space of the pharynx [69]. According to early reports, the single-port system could improve the accessibility and resection of tumors in the supraglottis and hypopharynx compared to previous versions without increasing the complication rate [70, 71].

The FLEX system developed by Medrobotics (Raynham, USA) is the second robotic system approved in the US and Europe for head and neck surgery (► **Fig. 3b**). The two systems differ fundamentally in the surgeon's handling and positioning. In the FLEX system, the





► **Fig. 1** Flexible endoscopic examination before and after transoral resection of an OPSCC of the left base of tongue base with TLM. **a.** Preoperative findings (white outline: tumor). **b.** After transoral tumor resection with fibrin layers and edema around the arytenoid cartilage five days after surgery. **c.** Swallowing examination with blue liquid: no sign of aspiration. (source: own images).



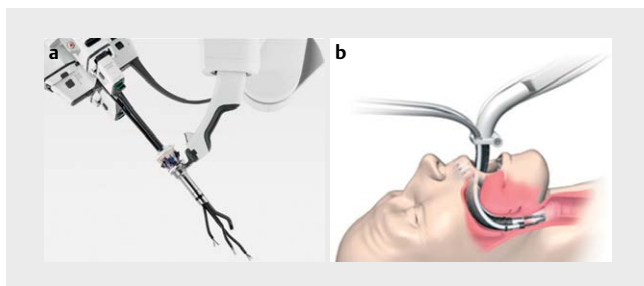
► **Fig. 2** Barium swallow after total laryngectomy. **a.** White arrow pointing to a fistula formation 10 days after surgery. **b.** Follow-up image 15 days after surgery without any detectable fistula formation. (source: own images).

surgeon is positioned at the patient's head and operates the effector instruments with their own hands, whereas the da Vinci system is controlled remotely. The FLEX instruments are inserted via working channels guided along a flexible, robotic endoscope, and the surgeon receives direct haptic feedback during surgery. 3D visualization is now also established for the FLEX system. Technical advancements in recent years have also included the development of special retractors [72], in order to improve the access to deeper anatomy such as the supraglottis and hypopharynx [73–75]. Both the da Vinci system and the FLEX system are primarily used for transoral oropharynx surgery, and less frequently in the supraglottis region or the hypopharynx. The glottis level or the nasopharynx are difficult to reach with the instruments and have to be considered borderline areas of application. Study results for the resection of tumors in these areas are on the level of single-case series. Studies

► **Table 2** The three most frequently applied questionnaires to assess the quality of life of head and neck cancer patients. QLQ-C30 and QLQ-H&N53: Questionnaire regarding the quality of life of the *European Organization for Research and Treatment of Cancer* (EORTC), UW-QOL: *University of Washington Quality of Life* questionnaire; MDASI-HN: *MD Anderson Symptom Inventory – Head and Neck Module* questionnaire.

Tool	Details
EORTC QLQ-C30/QLQ-H&N35	<ul style="list-style-type: none"> <li>Two modules of 30 and 35 items, respectively, general oncologic questions and specifically referring to head and neck cancer</li> <li>Scales of 0–100, higher scores correspond to better function as well as more symptoms</li> <li>5–10 points difference correspond clinically significant change [59–60]</li> </ul>
UW-QOL	<ul style="list-style-type: none"> <li>Surgeon's perspective, focus on post-therapeutic function</li> <li>15 items resulting in an overall score of 0 (poor) to 100 (good)</li> <li>6–7 points difference correspond to clinically significant change [61]</li> </ul>
MDASI-HN	<ul style="list-style-type: none"> <li>11 head and neck specific items, 13 general oncologic questions, 6 items about living circumstances (work, relationships etc.) [62]</li> <li>Assesses symptom burden, frequently used to evaluate time course of burden comparing different treatment modalities [63–64]</li> </ul>

on glottic laryngeal carcinomas resected with the da Vinci system show that the corresponding anatomical regions can be reached by flexible laser fibers without additional tracheostomy [76, 77], but also demonstrate difficulties in visualizing the anterior larynx-



► **Fig. 3** a. Da Vinci Single Port System (Intuitive Surgical, Sunnyvale, USA). b. FLEX-System (Medrobotics, Raynham, USA). (sources: courtesy of the manufacturers).

geal commissure and an increased risk of recurrence in this area [78]. Therefore, a standard expansion of the scope of robotic systems for glottic laryngeal surgery is not expected at this time, especially since excellent oncologic results have been achieved with TLM in this field for decades [79–81].

### 3.2 Other robotic assistance systems

In addition to the da Vinci system and the FLEX system with their main field of application in transoral surgery, a wide variety of robotic systems for head and neck surgery have been developed in recent years. Technologically, the systems differ fundamentally depending on the field of application, as the anatomical conditions dictate the focus of technical development. In the following, some systems for transnasal application in the area of the anterior skull base as well as for ear surgery are presented.

The robotic systems for transnasal applications in the region of the anterior skull base are generally not used as effectors, but function primarily as endoscope holders to improve visualization and allow the surgeon more freedom of action. These include the RO-VOT-m system (Synaptive Medical Corporation, Toronto, Canada), the Cirq system (formerly Endoscope Robot, Medineering Surgical Robots, Munich, now Brainlab AG, Munich, ► **Fig. 4**), and the SoloAssist endoscope system (AKTORmed Robotic Surgery, Barbing) [82–85]. In the systems, the endoscopes are attached to a carrier system and then inserted transnasally. Precise positioning is usually performed via joystick in multiple degrees of freedom. Robotic systems for transnasal use that have effector tools have not yet been used on patients but are in development. For example, the SmartArm system from the University of Tokyo in Japan, which has 3-mm-diameter flexible tools and a 4-mm-diameter endoscope. Good accessibility and effective treatment of anterior skull base defects have been demonstrated in cadaver studies [86]. A system from Vanderbilt University in the US is based on a system of microtubes designed to improve maneuverability and features instruments with a diameter of less than 2 mm [87, 88].

In contrast to robotic systems developed for transnasal access, which focus on size reduction and instrument maneuverability, the focus in robotic ear surgery is on increasing surgical precision. A common application example is electrode insertion for cochlear implant (CI) implantation. To avoid intracochlear trauma during insertion, traditionally implanting surgeons have had to rely on their subjective perception of resistance within the cochlea [89]. This



► **Fig. 4** Cirq System (Brainlab AG, Munich, Germany) used as an endoscope holder during endoscopic sinus surgery. (source: own images).

could be facilitated by the use of an insertion robot. In addition, conventional implantation involves extensive mastoidectomy, which could potentially be avoided by direct insertion channel drilling. For the systems used in ear surgery, Rijoas and co-authors propose a distinction between three classes of robotic systems [90], a) collaborative robotic systems, b) teleoperated systems, and c) autonomous systems. Collaborative systems have a limiting or reinforcing effect on the surgeon's continued manual instrument guidance. They guide the surgeon along a defined route and have been established in neurosurgery for some time, but in head and neck surgery they have only been tested in individual cases for precise, minimally invasive CI implantation [91]. Other systems limit the surgeon's deviation toward sensitive structures during surgery, for example by tracking the position of the drill intraoperatively using a navigation system. In the vicinity of previously defined structures, drilling speed is automatically reduced [92]. The Steady Hand Robot (Galen Robotics Inc., Baltimore, USA) reduces the surgeon's physiological hand tremor during ear surgery [93]. The teleoperated da Vinci system, which is primarily used in TORS procedures, has been used on an experimental basis in cadaveric studies for CI implantation [94], however, it has not yet been investigated in clinical use. Two alternative teleoperated systems from the University of Vanderbilt, USA, and the Technical University of Munich are expected to increase the precision of middle ear surgery and improve the accessibility of certain middle ear structures

[95, 96]. Clinical trials are expected. The RobOtol system (Collin Ltd., Begnuex, France) is approved for clinical application; it is used as instrument holder for endoscopic ear surgery [97] as well as an effector tool for the insertion of CI electrodes [98]. Fully autonomous systems are used in ear surgery for drilling in the mastoid, for example in CI implantation. The prerequisite is prior programming and continuous intraoperative position tracking, e. g., using infrared technology. Alternatively, the robotic system can be firmly connected to the patient's head [99]. Once appropriately programmed, the robotic systems can perform high-precision drilling procedures that are expected to make full mastoidectomy obsolete as part of CI implantation. The HEARO system (Cascination AG, Bern, Switzerland) is an example of such a fully autonomous system and has already been tested on patients [100]. For further information regarding the advantages and disadvantages of the clinically tested systems, see chapter 6.2.

## 4 The role of TORS in the treatment of oropharyngeal cancer

Currently, the transoral surgical treatment of oropharyngeal squamous cell carcinoma (OPSCC) is the main field of application for robotic surgical systems in head and neck surgery. The epidemiological changes in oropharyngeal carcinomas have contributed decisively to this trend in recent years: the incidence rates for OPSCC are increasing in absolute and relative terms compared to other head and neck tumors [101]. While exposure to the carcinogenic agents nicotine and alcohol is decreasing, thereby decreasing the likelihood of disease for the majority of head and neck squamous cell carcinomas, the increase in OPSCC in North America, Northern Europe, and Australia is due to the increase in the incidence of HPV-associated OPSCC [21, 102–106]. HPV-positive OPSCC are predominantly located in the lymphoid tissue of the tonsils and base of the tongue, which are accessible via TORS, and the response to therapy is significantly better than for HPV-negative carcinomas. This is true for both primary radiotherapy and primary surgical therapy [107–111]. The sharp increase in incidence in patients who tend to be younger and healthier with a high remaining life expectancy compared to non-HPV related OPSCC patients has led to the development and establishment of potentially less invasive treatment modalities: In the United States, patients with OPSCC were treated primarily with radiochemotherapy until the early 2000s. Because of the low prevalence of TLM, an external surgical approach to the

oropharynx was often chosen in the case of surgical therapy. Both procedures, radiation therapy and open surgery, are associated with a wide range of side effects. Despite a reduction in toxicity with the widespread adoption of intensity-modulated radiotherapy (IMRT), dry mouth and corresponding dysphagia are to be expected after high-dose radiotherapy. In addition, there is a risk of esophageal stenosis and osteoradionecrosis in the irradiation field [112, 113]. The introduction of the da Vinci system and the FLEX system for transoral resection of OPSCC provides a surgical alternative (► Fig. 5) that allows resection without open surgical approaches via lip-splitting, jaw-splitting, or an open transcervical approach. Thus, intra- and post-operative morbidity is reduced, and post-operative quality of life can potentially be improved. After a review of potential peri- and post-operative complications of TORS, the following sections present the value of TORS in OPSCC compared with the open surgical approach. This is followed by a comparison of TORS to primary radiotherapy, based on the available data concerning patient benefit and post-operative quality of life. Again, it should be noted that due to the pronounced regional differences in the spread of robotic technology, the majority of the results on TORS in OPSCC come from the US. A detailed comparison with TLM, which is more widely used in Germany and Europe and may offer similar advantages to TORS for certain indications, is not feasible due to the lack of data at this point.

### 4.1 Peri- and postoperative complications and side effects of TORS

For an initial assessment of the importance of TORS in the treatment of oropharyngeal carcinoma regarding patient benefit and quality of life, a brief overview of the risk profile of the surgical technique is indispensable. Peri-operatively, postoperative bleeding plays the greatest role, and post-operatively, swallowing difficulties have the most lasting impact on patients' quality of life. After almost two decades of experience, individual studies with large case numbers and meta-analyses are now available, which allow an assessment of the spectrum of complications and side effects.

#### 4.1.1 Postoperative bleeding

Postoperative bleeding is the most commonly documented complication during and after TORS procedures [114, 115]. The severity of postoperative hemorrhage can vary, so that depending on the definition of the reporting authors, postoperative hemorrhage rates range from 1.5% to 18.5% [116–122]. Pollei and co-authors



► Fig. 5 a-c: Transoral resection of an oropharyngeal carcinoma of the posterior pharyngeal wall with the FLEX system (Medrobotics, Raynham, USA). (source: own images).



proposed a classification system for bleeding events after TORS in 2013 to improve comparability [116] (► **Table 3**).

The classification system it is not consistently applied, however, following its grading allows for an estimation of the rate of major bleeding events; their rate ranges from 1.6 to 3.7% in the above-mentioned studies. Only in very rare cases does a fatal post-bleeding event occur; a multicenter U.S. study recorded a total of 4 cases with a fatal outcome, which corresponded to a rate of less than 0.2% of all patients examined in the study [114]. More than 80% of the documented bleeding events occurred within two weeks after surgery, and certain factors increase the risk for a bleeding event. These include surgery for recurrent disease or following prior radiation therapy, i. e., salvage surgery. Comorbidities and the use of anticoagulant therapeutics are also considered adverse factors. Interestingly, transcervical ligation of the feeding arterial vessels, which can be performed during neck dissection, does not seem to influence the overall rate of postoperative bleeding events. However, this prophylactic measure does have a significant limiting effect on the severity of bleeding events [116, 123]. Therefore, some authors recommend performing temporary tracheostomy if a neck dissection with vascular ligation is not performed as part of the tumor resection to prevent aspiration events in case of severe postoperative bleeding [124]. Although severe bleeding events are rare, the majority of bleeding events after TORS require surgical intervention, so they are classified as at least moderate according to Pollei and co-authors [125]. Most bleedings may be controlled by means of transoral monopolar cautery, and subsequent transcervical interventions are rarely necessary. Independent of patient-dependent factors, the experience of the treating surgeons affects the risk profile. Overall complication rates are lower in surgeons with high case volume, i. e., over 50 cases per year, than in those who perform TORS procedures less frequently [115]. This can be explained, among other things, by the fact that special instruments are used in TORS which are otherwise rarely used. With the help of special vessel clips for transoral ligation of fee-

ding arterial vessels, vessels with a diameter of more than 1 mm, can be safely ligated [126].

#### 4.1.2 Dysphagia

The extent of post-operative dysphagia plays a prominent role in the quality of life of patients after OPSCC therapy. It has been shown to be one of the strongest influencing factors on the extent of decision regret, i. e. retrospective second-guessing of the choice of therapy among patients [127]. Some studies provide an overview of the extent of swallowing difficulties in patients after TORS for OPSCC and can give an impression of the invasiveness of the procedure. It is important to note that many patients still receive adjuvant radiotherapy after primary TORS, which in turn may further adversely affect swallowing. A comparison of functional outcomes after TORS and primary radiotherapy is provided in section 4.3. Studies from the US and Europe show that, across all tumor stages, in approximately 5–8% of all cases after TORS in OPSCC patients, inpatient re-admission is required due to swallowing difficulties [121, 128, 129]. The extent of post-operative dysphagia after TORS without adjuvant therapy has been well studied, especially for patients with early tumor stages: Albergotti and co-authors, in a prospective study of patients with predominantly small primary tumors (96% stage T1 or T2), showed that 92% of patients were on a full oral diet at discharge, and 98% of patients were on an oral diet after 1 month [129]. Other studies in patients with early tumor stages, which examined swallowing ability at 6 and 12 months, also show good recovery of swallowing ability, at the latest 12 months after surgery [130, 131]. The duration of feeding via gastric tube after surgical therapy using TORS alone also suggests a favorable functional outcome: although a gastric tube is placed intraoperatively in up to 39% of patients, permanent tube feeding is required in only 0–9.5% of all cases [54, 121, 132–134].

#### 4.2 Surgery for oropharyngeal carcinomas: TORS vs. open resection

The goal of any surgical therapy for OPSCC is a complete resection of the tumor with adequate safety margins. This improves the overall prognosis of the patient, and the dose of adjuvant therapy administered depending on other risk factors can possibly be reduced [135]. HPV-positive OPSCC are particularly amenable to TORS because of their predominant localization in the tonsils or base of the tongue and their tendency towards lower T-stages at initial diagnosis compared with HPV-negative carcinomas [136]. However, patients with HPV-negative OPSCC may well benefit from the use of TORS for tumor resection [137, 138] if patients are carefully selected. Pre-operative imaging by CT or MRI plays an important role in treatment planning (► **Fig. 6**). Irrespective of the surgical approach, tumor tissue surrounding the internal carotid artery by 270° or more or an infiltration of the pre-vertebral musculature or the vertebral bodies are considered contraindications for primary surgery. Compared to open surgical approaches, local resection beyond the mandibular periosteum cannot be achieved by means of TORS, so that in cases of bony infiltration an open surgical procedure with subsequent reconstruction is more suitable [139]. The same applies to tumor infiltration of the masticator space, the pterygoid muscles or the temporalis muscle. Notably, the need for reconstruction using a free flap is not a contraindication for TORS

► **Table 3** Classification system for postoperative bleeding after TORS according to Pollei and co-authors [116]. Consistent application of a uniform classification system increases the comparability of studies.

Classification	Description
Normal	Bloody tinged sputum, bloody spots, brownish sputum, red streaks
Minor	Bright red blood or blood clots; resolved without surgery
Intermediate	Diffuse venous bleeding or minor arterial bleeding, surgery required, hemostasis by bipolar or monopolar coagulation
Major	Extensive hemorrhage requiring surgical intervention via transoral or transcervical vascular ligation or neuroradiologic intervention
Severe	Bleeding resulting in life-threatening medical complications such as airway obstruction requiring tracheostomy, cardiopulmonary arrest, hemodynamic instability requiring blood transfusion

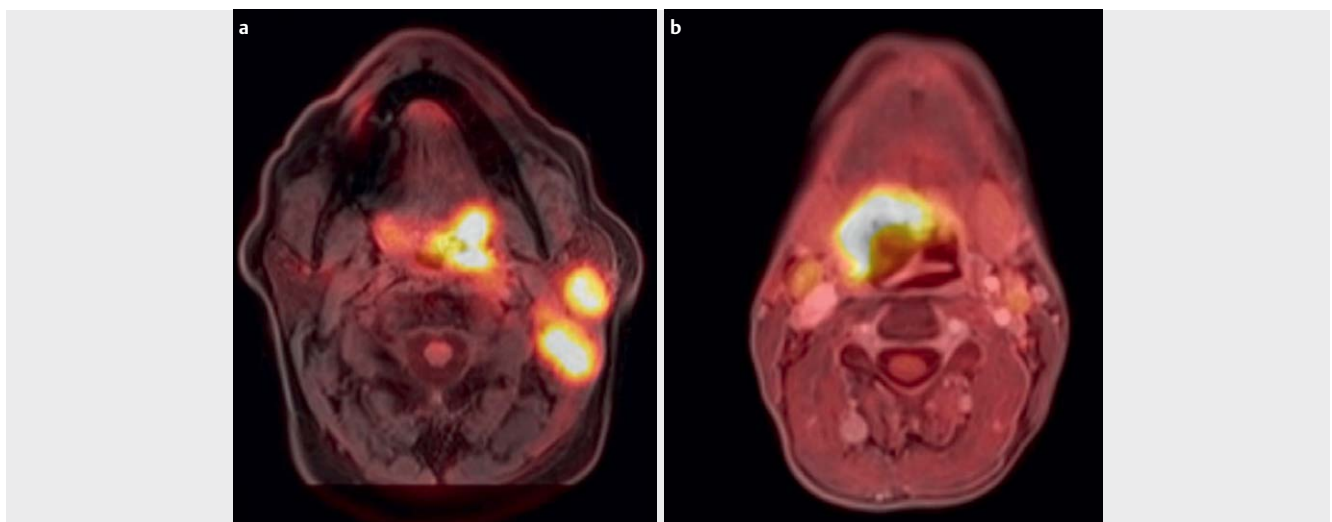
[140, 141]. However, if the parapharyngeal space is involved, the close relationship to the internal carotid artery and cranial nerves IX to XI must be considered, which may make transoral tumor resection difficult. Tumor manifestation in the nasopharynx is difficult to reach by TORS, especially the da Vinci system, and is typically reserved for open surgical approaches [142, 143]. In OPSCC of the base of the tongue, considerations regarding the depth of infiltration play a role: In case of tumor infiltration in the region of both lingual arteries, a higher degree of safety can be achieved with an open surgical procedure with regard to possible complications, but also the preservation of at least one supplying artery. In addition, immediate reconstruction is possible.

In cases where both resection via a transoral approach and an open approach are possible, advantages and disadvantages must be weighed. Here, aspects of the planned intraoperative procedure as well as their potential impact on post-operative function and quality of life play a role. The main advantages of an open approach for the resection of OPSCC, especially when performing a mandibular split, are the extensive exposure of the base of the tongue (► **Fig. 7**). Disadvantages of this highly invasive approach include the risk of postoperative malocclusion, postoperative infections, e. g., osteomyelitis, and, in the case of prior or adjuvant radiation, an increased osteoradionecrosis rate. Furthermore, osteosynthesis materials often have to be removed later on [144]. Aesthetic aspects, especially after lip split, must be taken into consideration [145]. With regard to the key patient benefit parameters, namely survival or cure rates, comparative studies suggest that there are no clear differences in oncologic outcome depending on the surgical approach, i. e., open vs. transoral [137, 146]. Individual studies, such as those by Ford and co-authors, do show a trend toward improved stage-adjusted and HPV status-controlled overall survival of patients after TORS compared with open surgery (94, 91, and 89% at 1, 2, and 3 years vs. 85, 75, and 73% at 1, 2, and 3 years, respectively) [137]. However, interpretation should consider that all studies were retrospective and thus non-randomized. Despite stage-adapted and HPV status-controlled analysis, it is conceivable

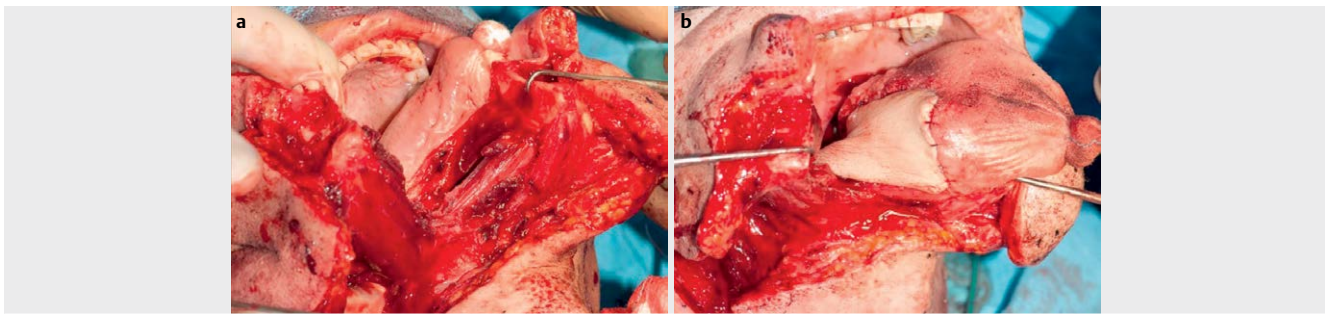
that with simultaneous availability of TORS and open surgery at individual centers, anatomically more critical tumor resections were more likely to be performed by open surgery. Whether this influences survival and cure rates in favor of TORS surgery is unclear, especially since overall tumor stages were considered in the analysis of the studies. However, at least with regard to functional quality of life parameters, influences in favor of robotic surgery by patient selection must be considered. Advantages of TORS over open surgery for OPSCC in terms of functional parameters were demonstrated by Lee and co-authors: Their study of patients with tonsillar carcinoma demonstrates a more rapid resumption of oral nutritional intake after TORS ( $6.5 \pm 4.2$  days compared with  $16.7 \pm 5.3$  days after open surgery), as well as a reduction in the average duration of tracheostomy by more than 8 days, with the TORS group also requiring less tracheostomies overall [147]. It has been shown that the hospitalization time of patients after TORS procedures is significantly shorter compared to open procedures. The duration until the start of adjuvant therapy is thus shortened, which in turn can have a positive effect on the prognosis [138]. The available data are limited; however, they allow the assumption that TORS provides advantages regarding the postoperative quality of life, especially in the context of important parameters like swallowing and tracheal cannula, compared to open approaches for well-selected patients. According to current knowledge, the key aspects of survival and healing are not negatively influenced after TORS in comparison to open surgery.

#### 4.3 TORS vs. primary radiotherapy: oncological outcome and quality of life

In the US, a paradigm shift has taken place in the last two decades: While in the early 2000s, only 54% of oropharyngeal carcinomas in early stages T1 or T2 received primary surgical treatment, by 2013, the rate increased to 82% of patients [148]. This trend is largely due to the establishment of TORS. Until the early 2000s, tumor resections in the oropharynx were predominantly performed via complication-prone transcervical or transmandibular approaches. A



► **Fig. 6** PET/MRI images. **a.** HPV positive oropharyngeal carcinoma of the left glossotonsillar fossa with large ipsilateral lymph node metastases. **b.** HPV negative oropharyngeal carcinoma of the left tongue base extending beyond the midline. (source: own images).



► **Fig. 7** Surgical access to the oropharynx by means of mandibular split. **a.** Extensive exposition of the body and base of the tongue. **b.** After reconstruction of the posterior right tongue with a radial forearm flap. (source: own images).

comprehensive 2002 study by Parsons and co-authors published in the journal *Cancer* suggested that oncologic outcomes were comparable after primary surgical therapy and primary radiation therapy. However, complication rates after primary surgical therapy in patients with OPSCC were significantly increased for both serious (25% for open surgery compared with 6% for primary radiation) and fatal complications (3.2% for open surgery compared with 0.8% for primary radiation)[149]. Although the definition of a "severe" complication was not uniformly applied in the above study, the results of this particular and other comparable studies shaped treatment preferences in North America in favor of primary radiotherapy for many years. In the case of primary surgical therapy, open approaches were preferred in the US, due in part to the low prevalence of TLM compared to Europe. In Europe, oropharyngeal carcinomas were routinely resected transorally using TLM as early as the 1980s [150]. In many US centers, TLM was introduced simultaneously to with TORS [151]. TORS subsequently gained increasing importance and has become established as standard therapy at many centers in recent years. Today, in the US, transcervical or transmandibular approaches are reserved for selected oropharyngeal tumors.

Compared to open surgery, transoral surgery offers advantages in terms of invasiveness and post-operative functional preservation when patients are well selected (see chapter 4.2.). However, this does not explain the shift in treatment preferences in favor of primary TORS compared with primary radiotherapy. Remarkably, the first prospective randomized trial comparing primary transoral surgery for OPSCC with primary radiotherapy was published as late as 2019. As previously outlined, such studies are difficult to perform when new surgical technologies are introduced, as their application is first investigated in selected patients. The Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR) trial is the first and only prospective randomized study to date comparing outcomes of the two treatment modalities in 68 patients. Treatment was either primary radiation (chemo)therapy or primary surgery with or without adjuvant radiation (chemo)therapy [152]. 88% of patients in both groups were HPV-positive patients and the primary end goal of the study was to assess patients' quality of life at one year after therapy. Oncologic outcomes were also recorded: The authors found no difference between the groups at 2 years in terms of both disease-specific survival and overall survival. In contrast, with regard to

post-operative quality of life the ORATOR study showed a statistically, but not clinically significant, difference in post-therapy swallowing ability in favor of primary radiotherapy. The MDADI questionnaire (see section 2.2.) was used as an assessment tool. Neutropenia, hearing loss, and tinnitus occurred more frequently in the radiotherapy cohort. Other retrospective studies also do not show any differences between primary TORS and primary radiotherapy in terms of cure and survival in OPSCC patients, the primary parameters for assessing patient benefit. In 2018, Sinha and co-authors presented a comprehensive meta-analysis. After reviewing 73 studies from 2001 to 2017, the authors concluded that the choice of primary therapy had no significant impact on recurrence-free survival or overall patient survival [153]. Only HPV status has a significant impact on patient survival independent of therapy: HPV negativity increases the hazard ratio for patients by 74% in the case of primary surgical therapy or by 64% in the case of primary radiotherapy. The results are thus in line with a previous, somewhat less comprehensive meta-analysis by Wang and co-authors [154].

Thus, the establishment of TORS for the treatment of OPSCC cannot be attributed to an improvement in the oncologic outcome of patients compared with radiotherapy. Rather, the focus is on the effort to positively influence patients' post-operative quality of life by reducing the adverse effects of surgery as much as possible. A direct comparison of post-therapeutic quality of life between patients after primary radiation and primary surgery is complicated by the fact that each therapy modality has a specific range of side effects. Surgery-specific risks include side effects associated with anesthesia as well as peri- and post-operative post-bleeding (see chapter 4.1.1.), which hardly play a role after primary radiotherapy. Radiation therapy-specific side effects include mucositis and fungal infections in the irradiated area; in the long term, xerostomia and fibrotic soft tissue changes play a role [155]. Nevertheless, the side effects of both forms of therapy affect patients' post-therapy swallowing ability, so most comparative studies focus on this key parameter.

In the prospective ORATOR trial, patients who had undergone primary radiation therapy had higher post-therapy MDADI scores than patients after primary surgery, and had better oral food intake ability one year after therapy [152]. It should be noted that the ORATOR data are based on a patient population of less than 30 patients per group. Further prospective studies are still ongoing (see below), so retrospective studies must be used for further as-

assessments at this time. In a meta-analysis, Yeh and co-authors compared a total of 44 retrospective studies of functional outcomes after primary radiotherapy or TORS in patients with OPSCC. They compared tracheostomy rates, duration of gastric tube feeding, and patients' swallowing ability, among other outcomes, as measured by different recording tools [156]. After primary IMRT, the tracheostomy rate was 0.1%–4.5% compared to 0%–3.5% after primary TORS. The rate of long-term gastric tube dependence after IMRT ranged from 0% to 18% with a mean of 6.1% and was significantly influenced by patient-dependent parameters of age, smoking status, lymph node status, and additional administration of chemotherapy [157]. In patients after primary TORS, the values varied between 0% and 20.7%, with a mean value of 3.8%. Regarding swallowing assessment, comparability is hampered by the variety of recording tools used. Only two retrospective studies compared patients after primary IMRT and primary TORS using standardized questionnaires, namely the MDADI questionnaire and the UW-QOL questionnaire, respectively (see section 2.2). More and co-authors demonstrated better functional swallowing ability after six months and one year, respectively, after primary TORS compared to IMRT using the MDADI [132]. Chen and co-authors also reported better outcomes after surgical therapy: After one year, the functional swallowing ability after TORS or TLM was significantly better compared to IMRT, measured with the UW-QOL (91.5 after TORS/TLM vs. 72.1% after IMRT) [158].

In summary, the data available to date do not suggest an advantage for patient survival for either of the two primary treatment modalities, TORS or IMRT. Statements on post-operative quality of life, especially patients' swallowing ability, vary: While the only available prospective randomized study shows benefits for IMRT, other retrospective studies demonstrate a benefit after primary TORS. Thus, currently, no advantages in terms of post-operative quality of life can be derived for either of the two primary forms of therapy. In the coming years, the results of several ongoing prospective randomized trials are expected, which might provide new insights due to larger numbers of included patients compared to the ORATOR trial. Three studies are summarized in ► **Table 4**, two of the studies use the MDADI as a tool to assess their primary end-

point and should provide detailed findings on post-operative swallowing ability.

When comparing post-operative quality of life after primary TORS versus primary IMRT, it should be noted that "primary TORS" in many cases nevertheless implies that patients subsequently received adjuvant radiotherapy. Most OPSCC patients are currently treated outside of HPV-status based de-escalation studies and often receive adjuvant therapy if lymph node metastases are present. Most of the patients included in the above studies were in fact treated even before the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual, which introduced a slight staging modification for HPV-positive OPSCC [159]. Because of the tendency of HPV-associated OPSCC to metastasize to lymph nodes early, adjuvant radiotherapy, sometimes with concomitant chemotherapy, was and is frequently applied in these patients [160]. In both above-mentioned retrospective studies and the prospective randomized ORATOR study, the proportion of patients who received adjuvant therapy after TORS was approximately 70% [26, 152].

Recent studies on OPSCC patients treated with TORS alone without adjuvant therapy show excellent post-operative results regarding swallowing function (see chapter 4.1.2). These are clearly superior to the average values of patients treated by primary TORS and adjuvant radiotherapy. Using various assessment tools, such as the DIGEST scale or the MDADI, values are often achieved as early as one month after surgery that are almost equivalent to the pre-operative values [161]. Thus, one could assume that treatment with TORS alone may lead to better functional outcomes compared to primary IMRT. Unfortunately, there are no studies comparing primary TORS alone with primary radiotherapy. Hence, the currently ongoing therapy de-escalation studies for HPV-associated OPSCC are all the more promising: If a comparable oncological outcome were shown for HPV-positive OPSCC patients using TORS alone, or possibly with reduced adjuvant therapy, compared to IMRT, primary surgical treatment could potentially be accompanied by a significant improvement in post-operative quality of life.

► **Table 4** Overview of selected prospective trials comparing primary TORS and primary IMRT for OPSCC.

Abbreviation	Title	Phase	Intervention	Primary outcome	NCT number
QOLATI	Quality of life after primary transoral robotic surgery vs intensity-modulated radiotherapy for patients with early-stage oropharyngeal squamous cell carcinoma: a randomized national trial	II	TORS and neck dissection ± radiochemotherapy vs. primary radiochemotherapy	Swallowing-related quality of life (MDADI)	04124190
Best of	Phase III study assessing the "best of" radiotherapy compared to the "best of" surgery in patients with T1-2, N0 oropharyngeal carcinoma	III	TORS, neck dissection vs. primary Radiotherapy and neck dissection	Swallowing-related quality of life (MDADI)	02984410
TopROC	Comparative effectiveness trial of transoral head and neck surgery followed by adjuvant radio(chemo) therapy vs. primary radio(chemo) therapy for oropharyngeal cancer	IV	TORS and neck dissection ± radiochemotherapy vs. primary radiochemotherapy	Recurrence-free survival and overall survival	03691441



#### 4.4 Role of TORS in therapy de-escalation for HPV positive oropharyngeal carcinomas

Patients with HPV-positive OPSCC tend to be younger and healthier at the time of diagnosis compared with patients with HPV-negative OPSCC; they therefore have a higher remaining life expectancy after therapy is completed [10]. Long-term side effects of therapy play a significant role in these patients. Therapy de-escalation studies aim to identify therapy modifications that reduce the side effect profile without compromising oncologic outcomes. Currently, prospective studies of both primary surgical and primary radiation-based therapy for HPV-positive OPSCC are underway. In many cases, TORS is used as the primary surgical therapy. Provided support by respective study results, the prospect of treating more advanced HPV-positive OPSCC with TORS alone or at least with reduced adjuvant therapy intensity opens up and patients' post-operative quality of life may be improved. Primary surgical therapy has an inherent advantage in the context of therapy de-escalation, namely that it enables definitive histopathologic staging of the primary tumor and the neck. This can be used to establish risk profiles that determine whether or not de-escalation of adjuvant therapy is feasible. Key factors are the number of metastatic cervical lymph nodes and any evidence of extracapsular extension (ECE) in these nodes. Cervical lymph node metastasis is a negative prognostic factor in HPV-positive OPSCC, but less impactful than in HPV-negative OPSCC [108, 162, 163]. In contrast, the prognostic role of ECE for HPV-positive OPSCC has not been conclusively established, and results from retrospective studies are conflicting. While some authors have demonstrated that ECE in lymph node metastases in HPV-associated OPSCC has no impact on prognosis [164–166], others found ECE to be risk factor warranting adjuvant therapy [167–170]. Most ongoing de-escalation studies still include ECE as an adjuvant therapy-determining factor in their study protocols.

Two prospective phase II therapy de-escalation studies with primary surgical therapy for HPV-associated OPSCC have already been completed and show promising results regarding oncologic outcome after intensity reduction of adjuvant therapy. In the AVOID trial, the primary tumor region in the oropharynx was excluded from adjuvant radiation in the case of complete prior TORS resection without additional pathologic risk factors such as perineural sheath infiltration or lymphatic vessel intrusion [171].

Irradiation of the neck was performed according to risk factors identified via bilateral neck dissection. Recurrence-free survival was 98.3% at two years for patients included in the single-arm study. The authors report that the tumor region was irradiated with only 36.9 Gy under the modified protocol. Regarding patient quality of life, the duration of gastric tube feeding was recorded and was 3.3% immediately after completion of reduced radiation and 0% after two years.

In the MC 1273 trial, the dose of adjuvant therapy after surgical tumor resection was reduced to 30 to 36 Gy depending on the patients' ECE status [172]. In the case of ECE detection, patients received 36 Gy of cervical irradiation; in addition, all patients in the study received docetaxel. In this study, a few tumor resections were performed via an open approach, but the portion of transoral resections was 95%. Recurrence-free survival at two years was 96.2%. The study authors report that no patient was fed via a gastric tube

one month after completion of therapy, and oral intake was largely unrestricted in all patients.

Final results from ECOG-E3311, also a phase II trial, are not yet available, but preliminary results were presented by the authors in 2020 [173]. In 519 OPSCC patients, all of whom were treated by primary TORS, adjuvant therapy was adjusted based on histopathologic results. Patients with complete or close margin tumor resection, two to four lymph node metastases, or ECE of one millimeter or less, were assigned to the intermediate of three risk groups and randomized to receive either 50 or 60 Gy of radiation. Patients with lower risk profiles received no adjuvant therapy, whereas patients with higher risk profiles received conventional therapy in the form of high-dose radiation chemotherapy. Remarkably, recurrence-free survival at two years did not differ when comparing all groups. Results regarding post-operative function and quality of life are not expected until the final publication of the data. Given the large number of patients included and the study design, very informative results are to be expected. Similarly, some other de-escalation studies investigating quality of life parameters as primary endpoints are underway. ▶ **Table 5** provides an overview of some of the relevant studies.

Aside from the above-mentioned studies on therapy de-escalation with primary surgical therapy, numerous studies on therapy de-escalation with primary radiotherapy are being conducted. If the therapeutic efficacy remains the same, a reduction in post-therapeutic morbidity and thus an improvement in the quality of life of the patients can be expected. This may then raise the question of the comparison between therapy-deescalated primary surgical therapy and therapy-deescalated primary radiotherapy. The ORATOR II study attempts to anticipate this by comparing a de-escalated radiotherapy-based treatment regimen, namely 60 Gy ± chemotherapy with primary surgical therapy ± adjuvant radiotherapy of 50–60 Gy (NCT03210103).

### 5 Special indications for TORS in the oropharynx: workup of cancers of unknown primary and treatment of obstructive sleep apnea

#### 5.1 Cancers of unknown primary

The term Cancer of unknown primary (CUP) refers to one or more cervical lymph node metastases of which the primary tumor site is unknown. CUPs account for approximately 1.5% – 9% of all head and neck carcinomas [174, 175]. In parallel with the increase in incidence of HPV-positive OPSCC, there has also been an increase in newly diagnosed head and neck carcinomas initially classified as CUP in recent years. After appropriate diagnostic workup, these often turn out to be HPV-associated OPSCC with a small, initially undetected, primary tumor and large cervical lymph node metastases [176, 177]. Identification of the primary tumor is challenging but, if successful, can significantly benefit patients by enabling targeted therapy of the primary tumor and associated metastases. Otherwise, extensive radiotherapy involving all likely primary tumor localizations in the head and neck region is required. Substantial post-therapeutic impairment is to be expected, for example pro-

► **Table 5** Overview of a selection of currently ongoing de-escalation trials on adjuvant therapy after TORS for OPSCC.

Abbreviation	Title	Phase	Intervention	Primary outcome	NCT number
DART-HPV	A phase III evaluation of de-escalated adjuvant radiation therapy for HPV-associated oropharynx cancer	III	Reduced radiotherapy (30–36 Gy according to risk profile) with Docetaxel vs. 60 Gy with Cisplatin	Complication rate	02908477
PATHOS	A phase III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for HPV-positive oropharyngeal cancer	III	Intermediate risk group: 50 Gy vs. 60 Gy; high risk group: radiotherapy vs. radiochemotherapy	Swallowing, overall survival	02215265
MINT	Phase II trial of surgery followed by risk-directed post-operative adjuvant therapy for HPV-related oropharynx squamous cell carcinoma: “the minimalist trial (MINT)”	II	Low risk: 42 Gy, intermediate risk: 42 Gy + Cisplatin once, high risk: 60 Gy + 3 doses of Cisplatin (standard therapy)	Weight loss during adjuvant therapy	03621696

nounced limitations in swallowing, xerostomia and extensive mucosal atrophy [178]. The widespread establishment of FDG-PET/CT in CUP diagnostics has improved the identification rates for primary tumors in CUP syndromes, but according to corresponding studies these rates are still below 50% without additional surgical diagnostics [179, 180]. For HPV-positive CUP, diagnostic surgery plays an important role. In the US, TORS is routinely used for this purpose and results are promising. If HPV-positivity is verified in the metastatic lymph node, a high probability of primary tumor localization in the oropharynx may be assumed. By means of a TORS palatal tonsillectomy and a TORS tongue base tonsillectomy, primary tumor detection has been shown to be successful in up to 89% of cases [181]. This also applies to patients with HPV-associated lymph node metastases where there is no evidence of a primary tumor localized in the oropharynx either on clinical examination or by imaging techniques such as conventional CT or PET/CT [182, 183]. Importantly, a complete tonsillectomy is considered superior to a biopsy for confirmation of the diagnosis. For identification of a primary tumor located in the area of the palatine tonsils, a meta-analysis showed a 10-fold increased odds ratio for successful tumor detection where a complete tonsillectomy was performed compared to a simple biopsy [184, 185]. Approximately 30% of previously undetected primary tumors in HPV-positive lymph node metastases are detected in the palatine tonsils, and over 60% in the base of the tongue, which is readily accessible by TORS (see Chapter 4) [186, 187]. The extent of diagnostic tongue base tonsillectomy by means of TORS should reach from the papillae circumvallatae to the vallecula and to the glossotonsillar fossae [188]. Notably, even in cases of unilateral lymph node metastases, the primary tumor may be located in the contralateral tongue base in 10% of cases, therefore bilateral diagnostic base of tongue resection is recommended [189]. The full extent of the procedure also increases the probability of a complete resection of the tumor during the diagnostic surgery. The rate of complete tumor resections after diagnostic TORS tongue base resection in the context of CUP syndrome has been shown to vary between 51% and 81% [189, 190]. Thus, compared with diagnostic imaging or biopsy sampling alone, diagnostic palatine tonsillectomy and tongue base tonsillectomy significantly increases the primary tumor identification

rate. In case of a complete surgical tumor excision, no further surgery of the primary tumor region may be required [191]. In any case, successful identification of the primary tumor reduces the extent of additionally required radiotherapy. The peri-operative risk profile of a tongue base tonsillectomy by TORS results mainly from the risk of post-operative bleeding, which is reported to be approximately 5% [182, 183]. One study revealed minor impairment of food intake one year after TORS for CUP, however, there were no cases of permanent feeding tube dependence or tracheostomy [192].

Similar to resection of OPSCC, it is not possible to assess whether TORS offers an advantage over TLM in CUP diagnosis based on the current data. Comparative studies are not currently available. However, some of the above-mentioned studies include TLM and show comparable data regarding primary tumor detection. Thus, it is most likely that transoral surgery has an overall benefit in the diagnosis and treatment of head and neck carcinomas initially classified as CUP syndrome, especially HPV-associated OPSCC with primary tumor localization in the base of the tongue.

## 5.2 Obstructive sleep apnea

In obstructive sleep apnea syndrome (OSA), apnea or hypopnea episodes occur while sleeping due to a collapse in the upper airway. Patients suffer from snoring, unrestful sleep and daytime sleepiness, and manifest OSA is also associated with an increased risk of cardiovascular disease [193]. The gold standard of OSA therapy is a continuous positive airway pressure (CPAP) mask [194]. About 30% of the patients do not tolerate the CPAP device so that surgical therapy may be taken into consideration. Recent data suggest that that selected OSA patients with a hypertrophic tongue base might benefit from surgical treatment with TORS if certain criteria are met [195]. Candidates for surgery should have primarily lymphatic, rather than muscular, tongue base hypertrophy; also, a purely latero-pharyngeal collapse should be ruled out via drug-induced sleep endoscopy [196]. An algorithm for identifying appropriate OSA candidates for tongue base reduction using TORS was developed by Lin and co-authors based on a study of 72 patients (► **Table 6**) [197]. A reduction of the apnea-hypopnea index (AHI)

of at least 50% and a post-therapeutic AHI below 15/h with reduced daytime sleepiness was defined as therapy response.

A recent meta-analysis of 31 studies showed a promising therapeutic response according to the above criteria of 69% after TORS in selected OSAS patients [198]. While no serious complications have been reported after TORS procedures in OSA patients, it should be noted that tongue base procedures can result in swallowing limitations. Paker and co-authors reported mild swallowing impairment in 32% of their treated patients in follow-up examinations 11 months after the procedure [199]. Overall, according to current knowledge, TORS for OSA is a procedure from which selected patients may benefit. Despite low complication rates, it is an invasive procedure with a specific risk profile that must be considered in patient selection and counseling.

## 6 Role of TORS for interventions in the larynx and hypopharynx

Structures anatomically located below the oropharynx, such as the supraglottis and glottis as well as the hypopharynx, present a greater challenge in terms of accessibility with the da Vinci system and the FLEX system. Although TORS for tumor resections in these in these anatomical regions areas is being investigated at some centers, it has not been established as standard therapy. Accordingly, mainly retrospective evidence from case series studies is available to date. Oncologic outcomes, complication rates, and quality of life assessments must be interpreted in this context: The patients included in the studies were usually specifically selected for the respective therapy, so that the parameters collected allow for an assessment of the potential patient benefit, but do not provide comparative data with respect to alternative forms of therapy.

► **Table 6** Algorithm for identification of suitable OSAS patients for reduction of the tongue base by means of TORS, according to Lin and co-authors [197].

Category		Score
Body-Mass-Index	<30	0
	30–40	1
	>40	2
Apnea-hypopnea index	<60	0
	>60	1
Lateral velopharyngeal collapse	No	0
	Yes	1
Therapy response to reduction of the tongue base by means of TORS according to the above-mentioned score (n = 72)		
0	86.7 %	
1	71.4 %	
2	25 %	
3	16.7 %	
4	0 %	

## 6.1 Supraglottic and glottic laryngeal carcinomas

Outside the oropharynx, TORS is most commonly used for the resection of supraglottic laryngeal carcinomas [200]. A recent meta-analysis by Lechien and co-authors on 422 patients with supraglottic laryngeal carcinomas showed good oncologic outcomes after TORS with the da Vinci system with 5-year recurrence-free survival rates of more than 90% [201]. In about 90% of the cases, the tumors were located in the area of the epiglottis or the aryepiglottic folds. 87.1% of included patients had stage T1 or T2 tumors at the time of surgery. Depending on the overall tumor stage, they received additional adjuvant radiotherapy. Prospective studies comparing TORS for supraglottic laryngeal carcinomas with open surgical procedures or primary radiotherapy are currently not available. However, retrospective comparisons suggest that for carefully selected patients, TORS offers equivalent oncologic outcomes compared with open surgery [200, 202]. Regarding peri- and post-operative complications, the above-mentioned meta-analysis reported a most likely aspiration-related pneumonia rate of 17.9%. Severe bleeding occurred in 6.9% of patients. The tracheostomy rate was 27.3%. While these data were gathered from surgeries using the da Vinci system, the tracheostomy rate in a study from the author's center on resection of supraglottic laryngeal carcinoma with the FLEX system was somewhat lower at 13%. We achieved excellent local tumor control rates over a 24-month follow-up period [74]. Functional data are scarce. Hans and co-authors report in a recent retrospective study of TORS for supraglottic laryngeal carcinoma using the da Vinci system that oral food intake was possible in 92% of the patients studied immediately after surgery. At the same time, the authors emphasize the risk for aspiration pneumonia after surgery, thus confirming the data of the above-mentioned meta-analysis by Lechien and co-authors [203]. While no studies comparing TORS for supraglottic laryngeal carcinoma with primary radiotherapy are available, some individual studies allow for an estimation of the significance of TORS compared to TLM. Regarding oncologic parameters, there seem to be no significant differences with regard to patient survival rates. The local tumor control rates tend to be slightly better after TORS compared to TLM, but the corresponding studies are not randomized, so that systematic errors in patient selection cannot be excluded [74, 204]. One could hypothesize that the use of TORS may improve three-dimensional visualization of a supraglottic tumor compared with TLM which is limited to one visual axis. A complete and ideally *en-bloc* resection may thus be easily feasible and contribute to improved local tumor control rates (► **Fig. 8**).

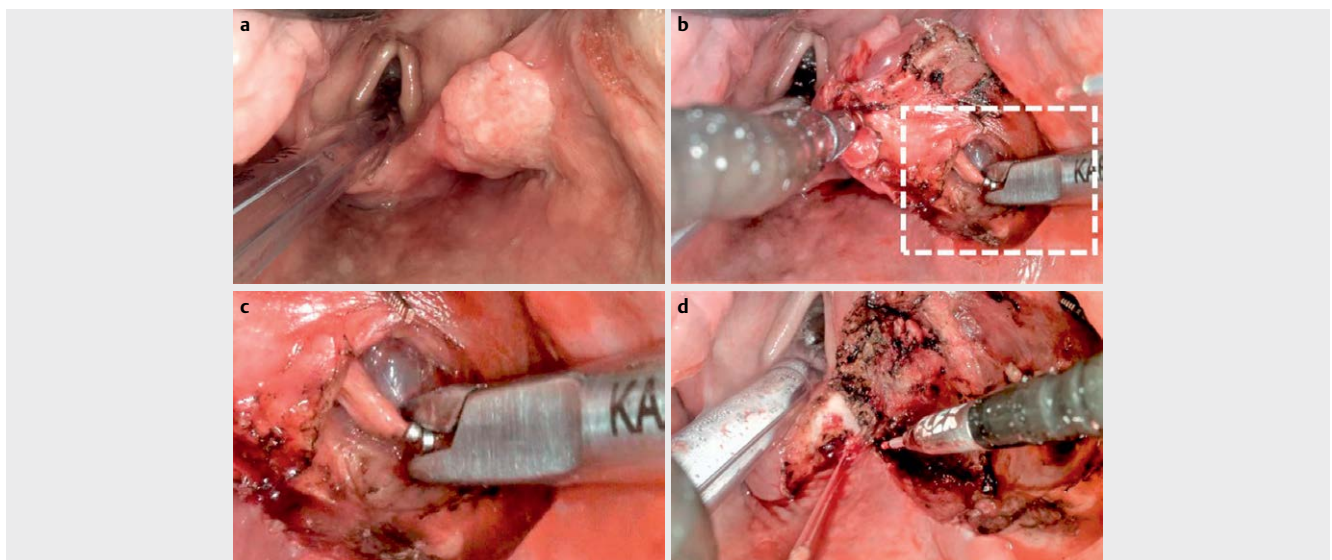
To date, TORS for the resection of glottic laryngeal carcinomas has been used predominantly in the context of feasibility studies. A US database analysis showed that from 2004–2014, less than 0.5% of all recorded glottic surgical procedures were robot-assisted [200]. Reaching the glottic level with robotic instruments is challenging depending on patient anatomy [205], at the same TLM is a well-established alternative transoral surgical method commonly used in Europe and some US centers. For stage T1 to T3 glottic laryngeal carcinomas, its use is associated with excellent oncologic and functional outcomes [79–81, 206]. To date, few oncologic and functional results are available after TORS for glottic laryngeal carcinomas, but the limited accessibility of the anterior

commissure in particular seems to lead to an accumulation of local recurrences and increased synechiae formation in this area [207]. The latter may also be due to increased thermal damage. Overall, the available data do not yet allow a definitive assessment of patient benefit, let alone post-operative quality of life after robotic surgery in the larynx. While the application in the supraglottic region may offer advantages in terms of tumor resection and thus oncologic outcome for selected patients, there is no evidence yet for advantages of the application of TORS in the glottic region compared to established therapeutic procedures.

## 6.2 Hypopharyngeal carcinomas

Over the past decade, primary TLM for hypopharyngeal carcinoma resection has been repeatedly shown to result in comparable oncologic outcomes compared with open surgery or primary radiation therapy [208–210]. Long-term preservation of the larynx is usually possible in this case. In contrast, open resection is often associated with complete laryngectomy and consequent loss of the natural voice due to the close proximity of the hypopharynx and the larynx and is associated with a significant loss of quality of life [211]. Due to the promising results in the above-mentioned studies related to transoral resection using TLM, investigations into the use of TORS for resection of hypopharyngeal carcinoma have been promoted in recent years. Potentially, the da Vinci system and the FLEX system could improve the visibility of the piriform sinus, the most common location of hypopharyngeal carcinoma, compared with TLM where the surgeon's view is limited to one visual axis. Similar to the use of TORS for supraglottic laryngeal carcinoma, there are currently no prospective studies comparing TORS with TLM or primary radiotherapy for hypopharyngeal carcinoma. However, some retrospective analyses of selected patient populations suggest that primary TORS can achieve at least comparable oncologic

outcomes to TLM, open surgery, and primary radiotherapy [133, 212, 213]. In the studies, which included a total of 112 patients, laryngeal preservation was possible over the follow-up period in more than 90% of the cases studied. Similar results were obtained using TLM [209]. Aside from organ and speech preservation, post-operative swallowing ability is of particular importance in patients with hypopharyngeal carcinoma with regard to quality of life. A standardized assessment of swallowing ability was performed by Park and co-authors, who demonstrated a FOSS score (see chapter 2.2.) of 0–2 (good outcome) in 76.3% of their total of 38 patients examined, while only one patient required permanent gastric tube placement. In the patient collective of Mazerolle and co-authors, too, only two of 57 patients permanently required a feeding tube [213]. Again, however, when interpreting the data, it should be noted that these are non-randomized studies with specifically selected patients. 66.7% and 98% of patients in the above-mentioned studies had primary tumors staged T1 or T2, respectively, at the time of surgery. While primary surgical therapy using TLM for early stage hypopharyngeal carcinomas is also associated with good functional outcomes [214–216], a direct comparison is not possible because different parameters were used for quality of life assessment. Thus, for the application of TORS in hypopharyngeal carcinomas, the following applies analogously to supraglottic laryngeal carcinomas: TORS is possible in selected patients and is associated with oncologic outcomes comparable to alternative surgical and nonsurgical therapies. Statements on the benefit for patients regarding post-operative quality of life are only possible to a limited extent - TORS in primary tumors at an early stage, however, seems to be associated with good post-operative swallowing ability.



► **Fig. 8** Transoral resection of a supraglottic laryngeal carcinoma of the right aryepiglottic fold with the FLEX system (Medrobotics, Raynham, USA). **a.** Before tumor resection. **b.** Intraoperative view. The superior laryngeal artery is ligated with a vascular clip. **c.** Magnified view of the marked area in B (white box) showing the vascular clips. **d.** View of the operative field after complete tumor resection. (source: own images; first published in *European Archives of Otorhinolaryngology* 2020 Vol. 277 Issue 3 Pages 917–924.).



## 7 Further application of robotic surgery in the head and neck

Further areas of application for robotic surgery in the head and neck region are presented below. For salivary gland and neck surgery, the da Vinci system is primarily used. For ear surgery, on the other hand, initial clinical results of the clinical application of the RobOtol system and the HEARO system are available.

### 7.1 Salivary glands and neck surgery

Robotic salivary gland surgery is usually performed transorally. For benign or malignant salivary gland tumors in the oropharynx, the resection is usually performed analogously to oropharyngeal carcinomas and is associated with a similar benefit/risk profile. By means of TORS, the parapharyngeal space can be accessed, for example, for the resection of pleomorphic adenomas, schwannomas, or cysts in this area [217]. Cosmetic aspects due to the avoidance of an external scar are mentioned as advantages of the transoral approach, and, if applicable, reliable identification and preservation of the facial nerve via the transoral approach seems possible [218]. In carefully selected patients, complete parapharyngeal tumor removal seems to be possible via the transoral route in a reliable manner. However, in a recent meta-analysis of transoral robotic resection of tumors of the parapharyngeal space, de Virgilio and co-authors reported that the tumor capsule was opened intraoperatively in 14.5% of the cases studied, and tumor fragmentation occurred in 10.3% of cases [219]. In 90% of the treated cases, the tumors were not malignant; however, pleomorphic adenomas were histologically detected in the majority of cases. These benign tumors have a high probability of recurrence if opened intraoperatively, therefore the above complication rates are unacceptable.

The main reason for robotic surgery in the soft tissues of the neck is the avoidance of a clearly visible external scar. Larger studies are now available, especially from Asia, describing the results of robotic-assisted surgery for cervical lymph node surgery and thyroid gland surgery. The access route is usually via a modified facelift approach from behind the ear. In a meta-analysis of a total of 655 patients, Sukato and co-authors show comparable results for robotic neck dissection with the da Vinci system compared to conventional neck dissection with regard to post-operative complications such as postoperative bleeding, chyle fistulas, nerve damage and wound infections [220]. While the number of lymph nodes removed did not differ between the two approaches, patients were more satisfied with the cosmetic outcome after robotic neck dissection. However, the duration of surgery was significantly longer and exceeded three hours for a modified radical neck dissection even after an appropriate learning curve after several years of surgical experience [221]. It should also be noted that, to date, no results are available regarding long-term oncologic outcomes after robotic-assisted neck dissection compared with the conventional approach. In addition to the improved cosmetic outcome, another potential benefit for patients is that the surgical scar is typically not located directly in the main radiation field in patients requiring adjuvant therapy, which may help to avoid any delays in the start of radiation due to wound healing problems [222]. However, to date, there are no reliable scientific data supporting this theory.

For robot-assisted thyroid surgery, an axillary approach can be used, which has been well-established in endoscopic thyroid surgery for about 20 years. This, too, is to avoid visible scars [223]. The trans-axillary approach is preferred in Asian countries and was adapted for robotic-assisted surgery early on, so that today there is copious data available on robotic-assisted thyroid surgery. Tumors larger than 5 cm, a body mass index > 35 kg/m<sup>2</sup> and thyroid diseases such as Hashimoto's thyroiditis or Graves' disease are considered contraindications for robot-assisted thyroid surgery [224]. Meta-analyses comparing the results of conventional thyroid surgery with the robotic-assisted approach show no differences in oncologic outcome or complication rates in large numbers of patients, especially with regard to iatrogenic damage to the recurrent laryngeal nerve [225, 226]. Consistently, however, all comparative studies show a significant prolongation of surgical time when using robotic technology for thyroid surgery.

For resections in the area of the submandibular gland, limited data on the use of robotic systems is available to date. In individual cases in which the da Vinci system was used for the resection of benign tumors, good cosmetic results were achieved; however, the duration of surgery was also significantly prolonged in this application compared with the conventional procedure [227].

In summary, robot-assisted salivary gland and neck surgery offers cosmetic advantages due to the access route, as an obvious scar can be avoided. However, comparable results can be achieved to some extent with established endoscopic techniques [228]. While longer-term oncologic results are already available for robotic thyroid surgery, it should be noted that, especially for robotic-assisted neck dissection, no final conclusions on the long-term impact on oncologic disease progression can be drawn at this point. Thus, an evaluation of the most important parameter for potential patient benefit, namely the impact on cure and survival, is still pending. In all areas of application, the use of robotic technology significantly prolongs the duration of surgery.

### 7.2 Ear surgery

Two robotic systems are currently being investigated in clinical trials for ear surgery, namely the RobOtol and HEARO systems from France and Switzerland previously introduced in chapter 3.2. So far, limited clinical data are available for both systems, yet their introduction is interesting in terms of patient benefit. Increasing surgical precision in ear surgery procedures has potential impact on post-operative hearing and thus patient quality of life.

The French RobOtol system is expected to help improve the surgeon's view during middle ear microsurgery procedures and also increase the precision of cochlear implant electrode insertion. In initial studies in middle ear surgery, the teleoperated system acted as an instrument holder for endoscopes. To avoid manual trauma to the ossicles and subsequent inner ear damage [229], the system was assessed regarding its benefit for an improved middle ear visualization [97]. Vittoria and co-authors report 21 cases in which the system was used in a feasibility study setting and the operations were performed successfully. Further studies comparing robotic-assisted surgery with conventionally performed procedures are currently pending. In addition, the RobOtol system has been studied in electrode insertion in adult and pediatric cochlear implantations [98, 230, 231]. Robotic insertion is expected to mi-

nimize intracochlear trauma and contribute to improved residual hearing preservation in patients. Preliminary results showed a lower dislocation rate for certain types of electrodes compared to manual insertion, potentially reducing insertion trauma. An assessment of the impact on functional outcome and potential benefit for patients is not yet possible due to the small number of cases and the varying baseline hearing ability of patients. Methodologically, a study by Jia and co-authors is interesting and therefore worth mentioning. The authors compared robotic insertion on one side and manual insertion on the other side in bilaterally fitted pediatric patients. However, since only six patients were included, no significant differences in post-operative hearing could be demonstrated to [231].

The HEARO system was developed for autonomous drilling of a transmastoidal approach to the middle and inner ear and subsequent robotic intracochlear cochlear implant insertion. In addition to a less invasive access route compared to manual implantation, which requires a mastoidectomy, the goal is to achieve the most atraumatic insertion of the electrode possible. Initial clinical feasibility studies show that the procedure was possible with the robotic system but could not be completed in all patients. In addition, the duration of surgery was significantly prolonged compared with the conventional approach [100, 232]. Comparative functional results are not yet available, so that an assessment of the potential patient benefit is pending.

## 8 Conclusion

A robust assessment of patient benefit and quality of life after robot-assisted head and neck surgery is currently possible for the use of TORS in oropharyngeal cancer resection. Here, extensive and long-term results are available, especially from the US. The basic requirements for the establishment of a new technology in the therapy of oncological diseases seem to be met: The primary patient benefit parameters cure and survival are not compromised compared to other forms of therapy, in this case open surgery and IMRT. The use TORS for the resection of oropharyngeal carcinoma appears to favor post-operative functional preservation compared to other treatment options, hereby potentially improving patients' quality of life. The study results reviewed in this article demonstrate that selected patients may benefit from TORS compared with open surgery, particularly with regard to post-operative swallowing ability. Compared with IMRT, TORS also appears to offer functional benefits, but primarily in cases of monomodal surgical treatment without adjuvant radiation. Notably, the majority of OPSCC patients currently still receives adjuvant therapy. Therefore, TORS as a primary treatment modality has a key role in ongoing treatment de-escalation trials for HPV-positive oropharyngeal cancer patients. In case of favorable study results, these patients with a high post-therapeutic life expectancy could benefit from the functional advantages of surgical therapy using TORS without, or with attenuated adjuvant radiotherapy.

In view of the increasing incidence of HPV-associated oropharyngeal carcinoma in Europe, both proportionally and in absolute terms, the low local prevalence of TORS use in Europe is surprising at first glance. This is most likely because in Europe, and particularly in Germany, TLM has been established for decades for the resec-

tion of oropharyngeal carcinomas and has been successfully established for the resection of oropharyngeal carcinomas with regards to oncologic and functional outcomes. In contrast, TLM never gained widespread acceptance in the US, and transoral procedures are now primarily performed using TORS. Unfortunately, comparative studies on TORS and TLM are currently hardly available due to the pronounced regional differences.

With regard to future studies on quality of life, the discrepancy between the multitude of available assessment tools, which are detailed at the beginning of the article, and their relatively rare use is remarkable. Many of the studies on the use of TORS in oropharyngeal cancer have focused on oncologic parameters and clinical indicators of quality of life such as duration of gastrostomy tube use or tracheostomy rates. Some ongoing treatment de-escalation studies are now using the appropriate tools to capture functional endpoints. The results could be used to provide a more detailed assessment of the different therapy modalities. In addition, the results may allow for an adaptation of therapy to individual patient preferences.

In the other application areas in the head and neck region, robot-assisted surgery is not established as standard treatment and is being evaluated at varying stages of clinical application. Longer-term retrospective studies are available for supraglottic TORS and robot-assisted thyroid surgery via external access routes. Here, selected patients may potentially benefit from its use in terms of functional and cosmetic aspects while maintaining oncologic outcomes. However, prospective studies comparing robot-assisted surgery with alternative therapeutic procedures are currently pending. The well-established da Vinci and FLEX systems are used for the above-mentioned non-oropharynx transoral and transcervical procedures. In contrast, robotic systems for ear surgery and paranasal sinus and skull base surgery are still in much earlier stages of development. Detailed statements on patient benefit and quality of life are not yet possible.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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