TORS in HPV-Positive Tumors—The New Standard?

S. Lang, S. Mattheis and B. Kansy

Abstract

In this chapter, we discuss implications of tumor site and tumor microenvironment properties of human papilloma virus (HPV)-associated cancer formation with special emphasis on the therapeutic modality of transoral robotic surgery (TORS). Over the past years, the development of robotic systems has improved, and therefore, its use in the surgical treatment of HNSCC has become a relevant treatment modality for many patients. Yet, there are limitations. Especially for endolaryngeal TORS procedures, additional technical development is mandatory, particularly with respect to visualization and manipulation. The Flex System has provided new additions that need to be further evaluated. TORS systems are going to improve technical issues and therefore reduce patient morbidity, surgical handling and treatment costs. The developed systems have to be tested and evaluated in prospective trials in order to be able to identify benefits and disadvantages in patient care. With respect to HPV-related OPSCC, TORS has become a valuable surgical alternative for an increasing number of patients.

Keywords

Transoral robotic surgery · TORS · Visualization · Manipulation · Oropharynx · da Vinci · Flex System

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W. Golusiński et al. (eds.), *HPV Infection in Head and Neck Cancer*,
Recent Results in Cancer Research 206, DOI 10.1007/978-3-319-43580-0_16

1 Introduction

During the past few decades, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has increased significantly (Tinhofer et al. 2015). This is mainly due to the rise in the incidence of human papilloma virus (HPV)-associated cancer formation in the oropharynx. Reasons for that have been widely discussed and commonly allocated to a change in sexual behavior, increased sexual promiscuity, and an earlier onset of sexual activities (Pytynia et al. 2014).

In the oropharynx, the reticulated squamous epithelium of the tonsillar tissue is characterized by a disrupted basilar membrane in order to facilitate the movement of lymphocytes and other cellular components of the immune system. These areas of physiological discontinuity of the basilar membrane have been proposed to be predilection sites for the entry of HPV (Best et al. 2012). Additionally, it has recently been shown that immune checkpoint ligands such as programmed death ligand-1 (PD-L1), which suppress overstimulation of immune responses, are overexpressed in the tonsillar crypts (Lyford-Pike et al. 2013; Pai 2013). Therefore, the crypts of the palatine and lingual tonsils in the oropharynx are considered to be the primary sites of HPV infection.

These unique tumor microenvironment properties, together with the location of the tumor site, i.e., oropharynx, have implications for both prognosis and therefore therapy of patients with OPSCC. In this chapter, we would like to discuss these implications with special emphasis on the therapeutic modality of transoral robotic surgery (TORS).

2 Anatomy of the Oropharynx and Implications for Surgical Approaches

The majority of HPV-associated head and neck squamous cell carcinoma (HNSCC) is located in the oropharynx. Anatomically, the oropharynx extends superiorly from the level of the hard and soft palate and inferiorly to the level of the hyoid bone, including anteriorly the base of tongue, vallecula, lingual surface of the epiglottis and posteriorly the pharyngeal wall comprising the superior and middle constrictor muscles and the buccopharyngeal fascia. The anterior and posterior pillars of the soft palate as well as the palatine tonsils represent the lateral limitations. The accessibility of the above structures differs intra- and inter-individually.

Therefore, surgical approaches depend not only on the tumor size, but also on the tumor location with important consequences for the following general aspects that have to be taken into consideration:

1. Complete tumor resection
2. Preservation of function
3. Minimization of cosmetic deformity
4. Plainness of technique

5. Cost-effectiveness

Usually, priorities decrease in the above-presented order, but have to be adjusted individually with respect to the patient's wishes and needs. These factors are dependent from an important surgical aspect: adequate exposure. Exposure of the oropharyngeal region can be achieved either by transoral (true transoral, pull-through, mandibulotomy) or by transcervical (pharyngotomy, laryngotomy and laryngectomy) approaches. Yet, for most oropharyngeal tumors (true) transoral approaches are the gold standard of surgery due to above-mentioned aspects. In the past decades, the transoral approaches have been augmented by the introduction of robot-assisted techniques, providing new modalities of tumor exposure and removal.

3 History of TORS

The use of robotics for surgical procedures started in 1985. The modified robotic device PUMA 200, originally from industrial background, was utilized to perform cerebral biopsies (Kwoh et al. 1988). Consequentially, the first medical robotic device for hip replacement surgery was developed, being able to drill the hip implant recess (Paul et al. 1992). This development led to a broadened use of robotic systems in surgery. Nowadays, there are two major systems that have been investigated and approved for the use in head and neck surgery (Remacle et al. 2015; O'Malley et al. 2006): The da Vinci® system (Intuitive Surgical Inc., Sunny vale, CA, USA) and the Flex® Robotic System (Medrobotics Corporation, Raynham, MA, USA). The da Vinci system was developed with the support of a research program at the Stanford University, California, in conjunction with the American Armed Forces. The goal was to establish a device that was able to perform remote-controlled surgery. A different company, Computer Motion Inc., initially developed two other robot types: Aesop and Zeus. Subsequently, both companies merged under the lead of Intuitive Surgical Inc. In 1997, a laparoscopic splenectomy was the first abdominal surgery assisted by the da Vinci system. Very soon, different procedures followed, such as gastrectomies, esophagectomies and prostatectomies. Altogether, the clinical feasibility was supported with positive reports concerning three-dimensional vision and surgical manipulation. Negative reports focused the missing tactile feedback and poor cost-effectiveness. In 2000, the FDA approved the da Vinci robot for human use (Himpens et al. 1998). The first study to describe the use of the da Vinci system in the cervical region in an animal model was performed by Haus and colleagues in 2003 (Haus et al. 2003). Ensuingly, Hockstein and Weinstein established a proof of feasibility in animal and human anatomical models at the University of Pennsylvania (Hockstein et al. 2005). This working group also established the term of transoral robotic surgery (TORS). The first-in-man study in the head and neck region was reported in 2005 by McLeod and Melder (2005). In the following years, the scope of application increased as the indications for TORS could be expanded. In the past years, a new robotic system, i.e., the Flex® Robotic System, was developed in order to enhance the spectrum of TORS and to overcome existing limitations. This system is specifically tailored to the needs of head and neck surgeons. In the head and neck region, the first resection of a benign tumor was reported by Remacle et al. (2015) and the first resection of a carcinoma by our team (Mattheis and Lang 2015; Mattheis et al. 2015). Both groups stated a safe and better access in comparison with the da Vinci device in more difficult to reach areas of the upper aerodigestive tract (Hasskamp et al. 2015).

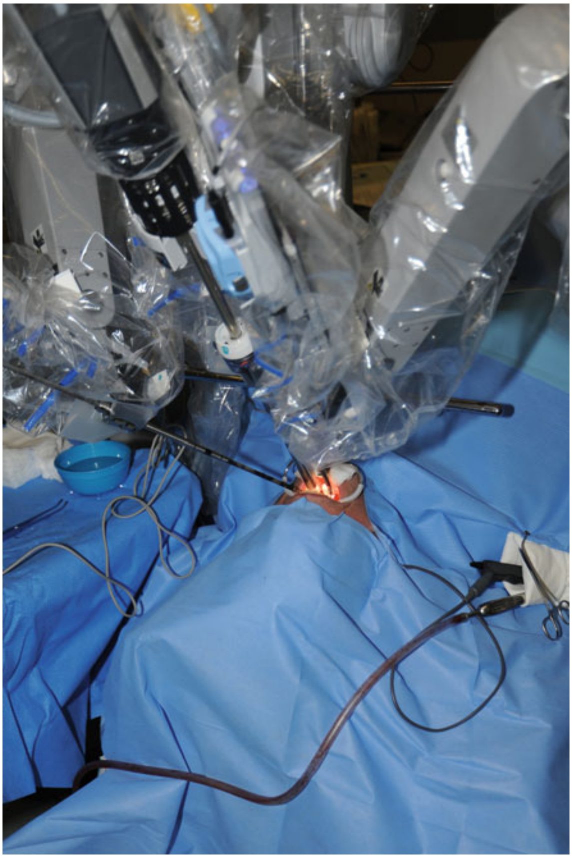
4 Different TORS Systems

The current and most frequently in HNSCC resections used da Vinci Si® system allows the surgeon to operate robotic arms through a steering console. The system is based on the console for the surgeon, separated from a unit with three robotic arms and a unit with an interactive monitor (Fig. 1). One of the robotic arms is equipped with a 3D HD endoscope camera (either 0° or 30°) in order to visualize the surgical field while the other two arms carry the surgical instruments (EndoWrist®, Intuitive Surgical Inc., Sunnyvale, CA, USA) (Fig. 2). These instruments offer a three-dimensional movement capacity and can be manipulated using a remote control connected to the surgeon's hands in the surgeon console (Fig. 3). Usually, one hand is steering the tissue retraction, while the other hand is responsible for cutting or further manipulation. The new da Vinci Xi® system presented in 2014 offers an enhanced mobility of the robotic arms and a more sophisticated HD camera, although the instrument diameter increased from 5 to 8 mm, thus making the access in the head and neck region difficult. Due to the fact that this system was originally developed for large cavity surgery, there has been no FDA approval for HNSCC yet.

With the Flex® Robotic System—developed specifically for transoral head and neck resections—the surgeon is able to insert a flexible endoscope into the pharynx. The endoscope can be advanced and steered in a sequential manner, alternating between a flexible and rigid state. Thus, the surgeon can define a path of approach that is not limited by line-of-sight access. Ultimately, the surgeon creates a self-supporting, stable platform from which he or she may visualize and operate (Fig. 4). An HD camera can transmit the pictures on a touch screen and on an external monitor. The surgeon controls the motion of the endoscope with a joystick on the Flex® Console which allows the surgeon to reposition or stabilize the endoscope anytime during the surgery (Fig. 5). There are two different, non-crossing, flexible working channels aside the endoscope for direct manipulation of flexible, fully articulating and rotating operating instruments. These instruments include a Flex® Laser Holder, Flex® Monopolar Maryland Dissector and Flex® Fenestrated Grasper for retraction and tissue manipulation, a Flex® Needle Driver for suturing, and a Flex® Monopolar Needle Knife, Flex® Monopolar Spatula, and Flex® Monopolar Scissor to cut tissue. When operating this system, the instruments provide the surgeon with direct tactile feedback.

Fig. 1 Da Vinci Si® system

Fig. 2 3D HD endoscope camera



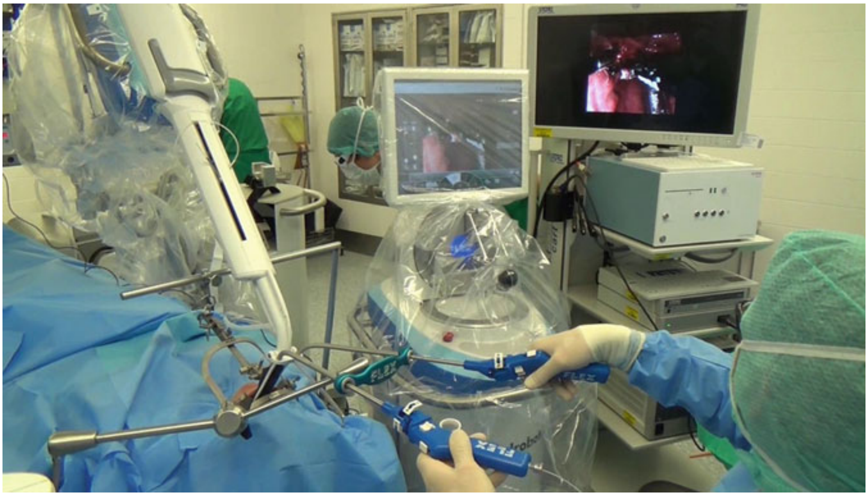


Fig. 3 Three-dimensional movement capacity

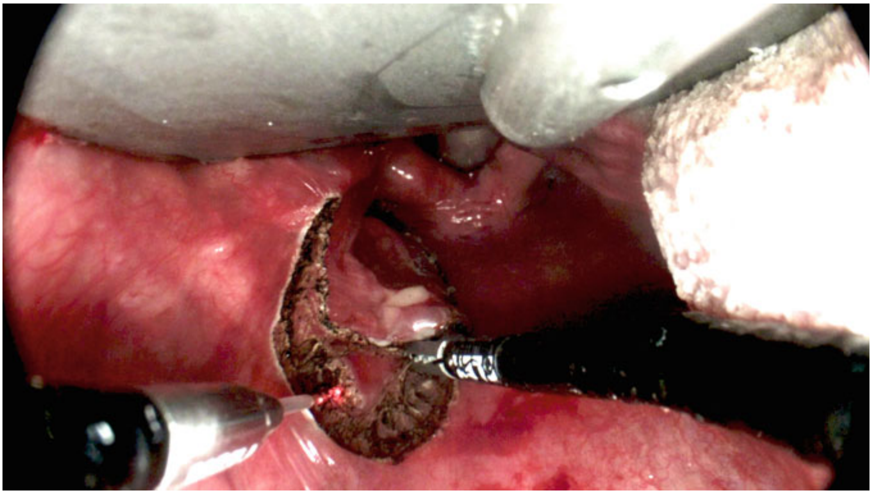


Fig. 4 Self-supporting, stable platform

Fig. 5 Flex® Console

5 The Use of TORS in Head and Neck Surgery

The goal of the surgical treatment of HNSCC is complete resection of the cancer with simultaneous preservation of the complex organ functions. Over the past few decades, transoral laser microsurgery (TLM) has been established as an important surgical concept and has become the gold standard for many HNSCC surgeons (Steiner 1994). This was due to comparable oncological outcomes after TLM treatment with reduced comorbidities and loss of function in comparison with classic open surgery techniques. After the introduction of robotic surgery, the systems were investigated with regard to surgical and patient benefits, including length of hospital stay, operating time, quality of surgical resection and quality of life for the patient compared to conventional surgery.

Over the past several years, the development of robotic systems has improved, and therefore, its use in the surgical treatment of HNSCC has become a relevant treatment modality for many patients.

After 2005, indications for TORS started to include the base of tongue (O'Malley et al. 2006), larger tumors of the pharynx (Weinstein et al. 2007) and the parapharyngeal space (O'Malley et al. 2010), tumors of the supraglottic area (Solares and Strome 2007) and the glottis (Desai et al. 2008). Choby and colleagues were able to demonstrate similar quality of life data in patients with OPSCC after TORS in comparison with other transoral surgical approaches and improved results in comparison with open surgery (Choby et al. 2015). Other data indicate an improved swallowing functionality for stage III and IV OPSCC after TORS in comparison with chemoradiotherapy (More et al. 2013). Additionally, different groups suggest the introduction of the TORS-assisted removal of base of tongue tonsil tissue for screening purposes in patients with cancer of unknown primary (CUP) syndrome (Mehta et al. 2013). Since CUP originating from oropharyngeal carcinomas is strongly correlated with HPV positivity, this becomes a particularly interesting aspect in regard to HPV-positive patients (Zengel et al. 2012). For resections of malignant lesions from the supraglottic and epiglottic regions using TORS, a local recurrence rate below 20 % has been reported (Mendelsohn and Remacle 2015).

Despite the enlarged spectrum of indications for TORS in HNSCC, there are limitations: One important factor is the accessibility of the region of interest. Although there have been reports about several glottic procedures (Smith 2014), the exposition of the narrow as well as delicate endolaryngeal structures is limited. Especially in comparison with conventional small endoscopes, the rigid, straight robotic arms, the bulky instruments and the short and broad retractors impair the accessibility (Mattheis et al. 2012). Additionally, in comparison with the crystal clear microscope-based visualization offered by TLM, the current cameras provide lower resolution and lower magnification resulting in reduced visualization of endoluminal structures. With the introduction of the Flex® Robotic System, some of these restrictions have been addressed. The combination with flexible instruments allows for a better accessibility of the relevant structures. Regions of the hypopharynx, especially the pyriform sinus, and regions of the larynx, e.g., the supraglottic region, can be simultaneously visualized, which helps in the assessment of possible infiltration of anatomical structures. The visual resolution remains inferior to the microscope of TLM. Surgeons positively report about the gained tactile feedback. Nevertheless, the system needs prospective clinical trials in order to validate its value and certify improvement in comparison with other established modalities, i.e., TLM.

With the technical advancements over the past few years, many of the early restrictions could be set aside leading to contraindications comparable to those for TLM procedures. Weinstein et al. grouped the contraindications into vascular, functional, oncologic and non-oncologic reasons (Weinstein et al. 2015): Vascular contraindications of TORS for oropharyngeal cancer include close vicinity to important arterial structures such as the carotid artery (e.g., by tumor encasement, or retropharyngeal course of the carotid artery in case of tonsillar cancer) or both lingual arteries (midline tongue base cancer). Functional contraindications include a required resection of more than 50 % of functional relevant structures such as deep tongue base musculature. Oncologic contraindications can result because of size and/or infiltration (T4b, prevertebral fascia), unresectable neck disease or distant metastases and neoplastic-related trismus. Finally, any non-oncologic conditions that prevent either any surgical approach in general or the specific transoral approach such as trismus or cervical spine disease limit the procedure. In our department, we are performing two-thirds base of tongue resections—irrespective of TORS—in selected cases.

Another important factor that potentially limits the use of TORS is the availability of these cost-intensive devices at the surgical centers. One of the main initial critiques of TORS was the high cost. This important factor in modern health care remains an issue. Dombrée and colleagues demonstrated that even in the case of well-trained surgical teams with short surgical times, the costs of the da Vinci system remain higher as compared to conventional surgical strategies in larynx procedures (Dombree et al. 2014). Other sources, however, report shorter periods of hospitalization and treatment-related costs, as well as patient morbidity, partially depending on the tumor location (Richmon et al. 2014; Chung et al. 2015). However, these results are from retrospective studies and their validity may be threatened by biases in areas such as patient selection. In general, additive to the costs of open surgery or TLM, which are mainly determined by personnel, surgical time and hospitalization, the costs of TORS-assisted procedures are also determined by high acquisition costs and the maintenance. This aspect potentially limits the distribution in institutions that are involved in the primary care of HNSCC patients.

6 TORS in HPV-Positive Patients

TORS has demonstrated advantages for a better visualization of the pharynx, especially at the base of tongue. In HPV-related carcinoma, the base of tongue as part of the oropharynx is frequently involved. Surgeons (and therefore patients) potentially benefit from an increased mobility and a better overview in comparison with conventional TLM. In comparison with chemoradiotherapy, TORS has been associated with lower morbidity rates and better functional outcomes. Still, the decision for or against the surgical treatment lies at the end of an interdisciplinary team-based approach including the patient's individual wishes and needs. Therefore, after the decision for surgical treatment has been made, it must then be determined if TORS is indicated. So far, HPV testing is not yet a prognostic predictive marker for a certain established therapeutic alternative and therefore should not change management decisions except in the context of a trial, yet a majority of US physicians report an influence of HPV testing on their treatment approach for OPSCC (Maniakas et al. 2014). As reasons were not given in this survey, one can only speculate that HPV testing may lead to a de-intensification of therapy in the case of HPV-positive test results. To what extent that the TORS procedures will play a role in de-intensification for HPV-positive patients needs to be further evaluated, as the technical development will continue and trials for de-intensification strategies are ongoing.

7 Conclusion

TORS is a valid alternative for surgical transoral procedures in selected cases. Especially for endolaryngeal TORS procedures, additional technical development is mandatory, particularly with respect to visualization and manipulation. The Flex® Robotic System has provided new capabilities that need to be further evaluated. TORS systems are going to improve technical issues and therefore reduce patient morbidity as well as improve surgical handling. The developed systems have to be tested and evaluated in prospective trials in order to be able to identify benefits and disadvantages in patient care. With respect to HPV-related OPSCC, TORS has become a valuable surgical alternative for an increasing number of patients.

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