ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:

‘‘ΕΛΑΧΙΣΤΑ ΕΠΕΜΒΑΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ,

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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ:

"A REVIEW FOR INDICATIONS IN TRANSORAL ROBOTIC SURGERY IN OROPHARYNGEAL CANCER"

ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑ:

ΚΑΡΑΜΑΛΗ ΚΑΤΕΡΙΝΑ

Α.Μ. : 20130757

ΑΘΗΝΑ, ΜΑΪΟΣ 2016

ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ

ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

Της Μεταπτυχιακής Φοιτήτριας ΚΑΡΑΜΑΛΗ ΚΑΤΕΡΙΝΑΣ

Εξεταστική Επιτροπή

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- Θεόδωρος Διαμαντής, Ομότιμος Καθηγητής Χειρουργικής

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της.....[ης] .... 20.... για την αξιολόγηση και εξέταση της υποψήφιας κας Καραμαλή Κατερίνας, συνεδρίασε σήμερα .../.../....

Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία της κας Καραμαλή Κατερίνας με τίτλο: «*A review for indications in transoral robotic surgery in oropharyngeal cancer»* είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ' όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους .... προτείνει την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's Degree), στην παραπάνω Μεταπτυχιακή Φοιτήτρια.

Στην ψηφοφορία για την βαθμολογία η υποψήφια έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ...., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ...., και για τον βαθμό «ΚΑΛΩΣ» ψήφους .... Κατά συνέπεια, απονέμεται ο βαθμός «.....................».

Τα Μέλη της Εξεταστικής Επιτροπής

- Ιωάννης Γκρινιάτσος, **(Επιβλέπων)** (Υπογραφή) ________________
- Χρήστος Π. Τσιγκρής, (Υπογραφή) ________________
- Θεόδωρος Διαμαντής, (Υπογραφή) ________________

Στην οικογένειά μου με αγάπη …

Στη Χαρά …

Στην Αγγελική…

Στην Κα Κώνσταντου για την υποστήριξη...

Στους Καθηγητές μου με σεβασμό…

Σε όσους ονειρεύονται και προσπαθούν για μια καλύτερη εκπαίδευση στη Χειρουργική και την Ιατρική στον Ελληνισμό…

ΙΠΠΟΚΡΑΤΟΥΣ ΟΡΚΟΣ.

HIPPOCRATIS IVSIVRANDVM.

ὈΜΝΥΜΙ [2] Ἀπόλλωνα ἰητρὸν καὶ Ἀσκληπιὸν καὶ Ὑγείαν καὶ Πανάκειαν, καὶ θεοὺς πάντας καὶ πάσας, ἵστορας ποιεύμενος, ἐπιτελέα ποιήσειν κατὰ δύναμιν καὶ κρίσιν ἐμὴν, ὅρκον τόνδε καὶ ξυγγραφὴν τήνδε. [3] ἡγήσασθαι μὲν τὸν διδάξαντά με τὴν τέχνην ταύτην, [4] ἴσα γενέτῃσιν ἐμοῖσιν, καὶ βίου κοινώσασθαι καὶ χρεῶν χρηΐζοντι μετάδοσιν ποιήσασθαι. καὶ γένος τὸ ἐξ ἑωυτέου, ἀδελφοῖς ἴσον ἐπικρινέειν ἄῤῥεσι. καὶ διδάξειν τὴν τέχνην ταύτην, ἢν χρηΐζωσι μανθάνειν, [5] ἄνευ μισθοῦ καὶ ξυγγραφῆς. [6] παραγγελίης τε καὶ ἀκροήσιος, καὶ τῆς λοιπῆς ἁπάσης μαθήσιος, μετάδοσιν ποιήσασθαι υἱοῖσί τε ἐμοῖσι, καὶ τοῖσι τοῦ ἐμὲ διδάξαντος. καὶ μαθηταῖσι συγγεγραμμένοισί τε, καὶ ὡρκισμένοις νόμῳ ἰητρικῷ. ἄλλῳ δὲ οὐδενί. διαιτήμασί τε χρήσομαι, ἐπ᾽ ὠφελείῃ καμνόντων κατὰ δύναμιν καὶ κρίσιν ἐμήν. [7] ἐπὶ δηλήσει δὲ καὶ ἀδικίῃ εἴρξειν. [8] οὐ δώσω δὲ οὐδὲ φάρμακον οὐδενὶ αἰτηθεὶς, θανάσιμον. οὐδὲ ὑφηγήσομαι ξυμβουλίην τοιήνδε. ὁμοίως δὲ οὐδὲ γυναικὶ πεσσὸν φθόριον δώσω. ἁγνῶς δὲ καὶ ὁσίως διατηρήσω βίον τὸν ἐμὸν καὶ τέχνην τὴν ἐμήν. οὐ τεμέω δὲ οὐδὲ μὴν λιθιῶντας. [9] ἐκχωρήσω δὲ ἐργάτῃσιν ἀνδράσι πρήξιος τῆσδε. εἰς οἰκίας δὲ ὁκόσας ἂν ἐσίω, ἐσελεύσομαι ἐπ᾽ ὠφελείῃ καμνόντων, ἐκτὸς ἐὼν πάσης ἀδικίης ἑκουσίης καὶ φθορίης τῆς τε ἄλλης [10] καὶ ἀφροδισίων ἔργων, ἐπί τε γυναικείων σωμάτων [11] καὶ ἀνδρώων, ἐλευθέρων τε καὶ δούλων. ἃ δ᾽ ἂν ἐν θεραπείῃ ἢ ἴδω, ἢ ἀκούσω, ἢ καὶ ἄνευ θεραπείης κατὰ βίον ἀνθρώπων, ἃ μὴ χρή ποτε ἐκλαλέεσθαι ἔξω, σιγήσομαι, ἄῤῥητα ἡγεύμενος εἶναι τὰ τοιαῦτα. Ὅρκον μὲν οὖν μοι τόνδε ἐπιτελέα ποιέοντι, [12] καὶ μὴ ξυγχέοντι, εἴη ἐπαύρασθαι, καὶ βίου καὶ τέχνης, δοξαζομένῳ παρὰ πᾶσιν ἀνθρώποις, εἰς τὸν ἀεὶ χρόνον· παραβαίνοντι δὲ καὶ ἐπιορκοῦντι, τἀναντία τουτέων.

PER Apollinem Medicum, & Æſculapium, Hygiamque & Panaceam iureiurando affirmo, & Deos Deasq; omnes teſtor, me quantum viribus & iudicio valuero, quod nunc iuro, & ex ſcripto ſpondeo planè obſeruaturū. Præceptorem quidem qui me hanc artem edocuit, parentum loco habiturum, eique cùm ad victum, tum etiam ad vſum neceſſaria, grato animo communicaturum & ſuppeditaturum. Eiusque poſteros apud me eodem loco quo germanos fratres fore, eosque ſi hanc artem addiſcere volent, abſque mercede & ſyngrapha edocturum. Præceptionum quoque & auditionum, totiusque reliquæ diſciplinæ, cùm meos & eius qui me edocuit liberos, tum diſcipulos qui Medico iureiurando nomen fidemque dederint, participes facturum, aliorum præterea neminem. Victus quoque rationem, quantum facultate & iudicio conſequi potero, ægris vtilem me præſcripturum, eosq; ab omni noxia & iniuria vindicaturum. Neq; cuiuſquam precibus adductus, alicui medicamentum lethale propinabo, neque huius rei author ero. Neque ſimili ratione mulieri peſſum ſubditium ad fœtum corrumpendum exhibebo: ſed caſtam & ab omni ſcelere puram, tum vitam, tum artem meam perpetuò præſtabo. Neque verò calculo laborantes ſecabo, ſed magiſtris eius artis peritis id muneris concedam. In quancunque autem domum ingreſſus fuero, ad ægrotantium ſalutem ingrediar, omnem iniuriæ inferendæ & corruptelæ ſuſpicionem procul fugiens, tum vel maximè rerum venerearum cupiditatem, erga mulieres iuxta ac viros, tum ingenuos, tum ſeruos. Quæ verò inter curandum, aut etiam Medicinam minimè faciens, in communi hominum vita, vel videro, vel audiero, quæ minimè in vulgus efferri oporteat, ea arcana eſſe ratus, ſilebo. Hoc igitur iuſiurandum ſi religiosè obſeruaro, ac minimè irritum fecero, mihi liceat cum ſumma apud omnes exiſtimatione perpetuò vitam fœlicem degere, & artis vberrimum fructum percipere. Quòd ſi illud violauero & peieraueró, contraria mihi contingant.

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1. INTRODUCTION

1.1 Anatomic bounders of Oropharynx

The anatomic bounders of oropharynx include: anterosuperiorly the junction of the hard and soft palate, anteroinferiorly the circumvallate papilla, and anterolaterally the posterior aspect of the palatoglossal muscle or the anterior palatine arch (1). The superior boundary is defined at the level of the hard palate and the inferior boundary at the level of the pharyngoepiglottic folds (1). The subsite can be further divided into the soft palate, lateral and posterior pharyngeal walls, tonsillar complex and base of tongue.

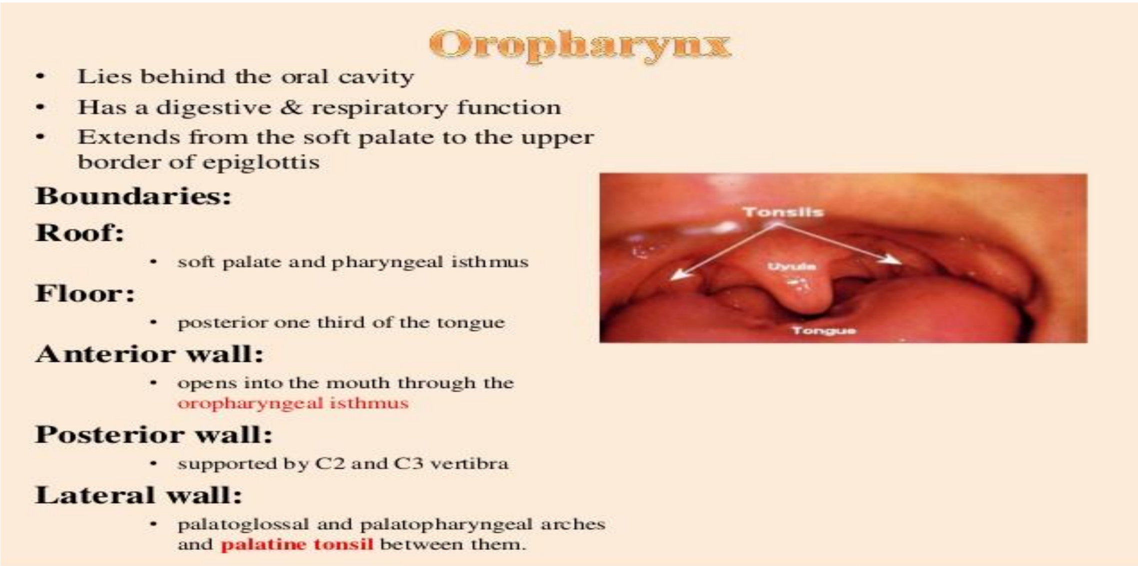


Figure 1: The anatomic bounders of Oropharynx

1.2 Demographic elements

According to epidemiological studies, there has been an increase in the incidence of oropharyngeal cancer, while correspondingly; oral cavity cancer incidents remain constant in numbers. These deviating trends can be explained by a virus, the human papilloma virus, which advantageously targets the oropharynx.

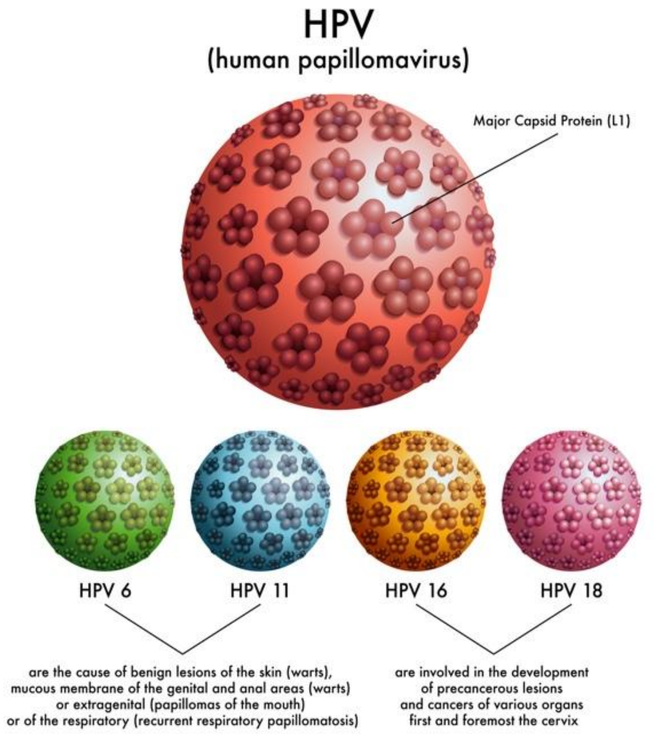


Figure 2: The human papilloma virus. There are many types of this virus and almost a hundred have been identified.

Approximately 5000–9000 new incidents of oropharyngeal cancer occur in the United States every year (2-4). Based on published studies, the disease will finally claim over 70,000 lives annually all over the world (5). The rate of occurrence of tongue based, as well as tonsil based cancers is about 2 in 100,000 (3).This rate is increasing by 2.1% and 3.9% respectively every year (6). This tendency directly contradicts the diminishing incidence of other aerodigestive cancers and is also widely accounted for by patients of younger age who also have little, if any, history of tobacco use (6, 7). Therefore, it has been implied that Human papilloma virus (HPV) is the main causative factor.

1.3 Transoral Robotic Surgery (TORS)

The Da Vinci surgical system consists of a surgeon console and a surgical cart. The surgical cart has two laterally placed instrument arms and a centrally located endoscopic arm holding the 3D camera which is positioned at 30 to 45 degrees angle adjacent to the operating table. The surgeon sits on the console a few feet away where, through the console controls, he operates the robot instrument and views the surgical field through the 3D camera. The patient is intubated with laser safe tube. The head of the patient is to be at an 180o angle from the anaesthetic machine and the eyes have to be protected (8). Access to the oropharynx is achieved with a Crowe

Davis retractor, a Dingman retractor or a Feyh-Kastanbauer retractor which is suspended from the arm fastened on the bed. A combination of the two cameras (0^o and 30^o) gives the perception of 3D view. Different instruments could be used on the lateral arms, such as needle drivers, bipolar forcep, and Maryland forceps. Variety of cutting instruments have been used like flexible carbon dioxide CO_2, laser with 20 W nova pulse laser to complete the surgical resection because has the benefit to cut mucosal and muscular tissue without causing severe damage to peripheral tissue.

The da Vinci Surgical System provides a 3-dimensional magnified view, reduces hand-tremor, is supplied with fine-motion scaling, and administers precise and multi-articulated motion.

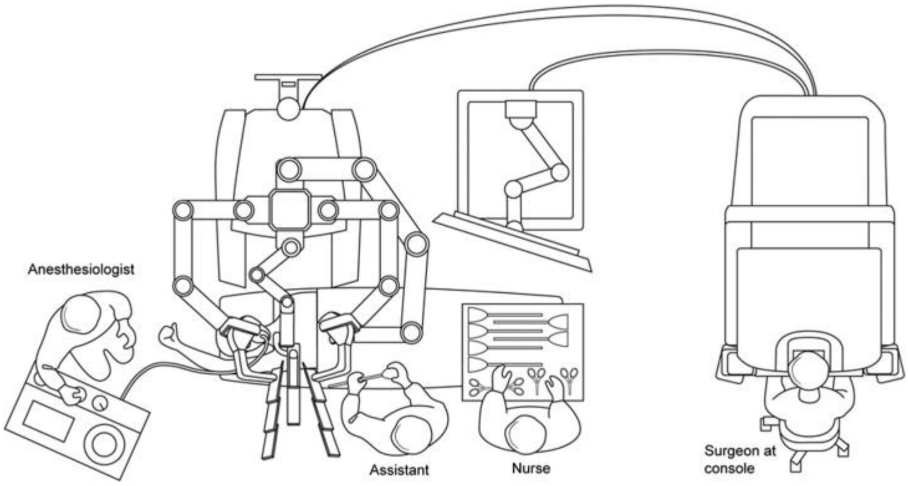


FIGURE 3: Introduction angles of the robotic arms; the external three joints of the robotic arms should form an inverted triangle.

In 2009, the Food and Drug Administration approved this procedure for T1 to T2 oropharyngeal cancers. However, the role of the Da Vinci robot has increased dramatically because of additional developments and refinements, and it has been used for a wide range of procedures in the head and neck.

FIGURE 4: Port placement and instrument insertion.

2. A BRIEF HISTORY OF TORS

The Da Vinci system was utilized in Otolaryngology in 2005 for the first time. Mcleod et al. from the Walter Reed Medical Center WA, USA (9), as well as Hockstein et al. from the University of Pennsylvania (10) were the pioneers of the method. Cadavers were used as the first experimental procedures were commenced. Both teams carried out laryngeal procedures and reached the conclusion that the Da Vinci Surgical system was superior to TOLM, not only in terms of safety, but also accessibility. Thus, the term "transoral robotic surgery- TORS" was coined.

Hockstein et al. from the University of Pennsylvania further researched TORS, in order to evaluate the extent of its efficacy and safety regarding pharyngeal and microlaryngeal lesions (11). After performing a partial resection of the base of the tongue, the results showed that TORS allowed for unimpeded instrument mobility, better exposure, superior delicate handing of tissue and duration of procedure relative to that of the open conventional methods. Macleod et al. performed a vallecular cyst resection the same year. During the next year, O'Malley et al. (12) performed ten resections on the base of the tongue by using cadavers. The same procedure was also used on live mongrel dogs.

Figure 5: Head & Neck Surgery – The da Vinci Transoral Robotic Surgery (TORS)

3. ROBOTIC ANATOMY

3.1 The robotic prospective of the oropharyngeal anatomy (13)

Robotic surgery requires a different prospective when approaching an oral cavity or the pharynx, compared to the traditional open surgery. The robotic surgeon is able to rotate the magnified view and change its angles, depending on the type of endoscope utilized. All threse conditions may increase the technical difficulty of the surgery, eventhough the use of a 3-dimensional endoscope bypasses the flattening effect that occurs with traditional endoscopes.

The oropharynx has its anatomic boundaries: anterosuperiorly the junction of the hard and soft palate, anteroinferiorly the circumvallate papilla, and anterolaterally the posterior aspect of the palatoglossal muscle or the anterior palatine arch. The superior boundary is located at the region of the hard palate and the inferior boundary at the level of the pharyngoepiglottic folds. The subsite can be further divided into the soft palate, lateral and posterior pharyngeal walls, tonsillar complex and base of tongue.

In this area the neurovascullar and muscullar relationships are important when a surgeon is willing to perform tongue base resections and radical tonsillectomies.

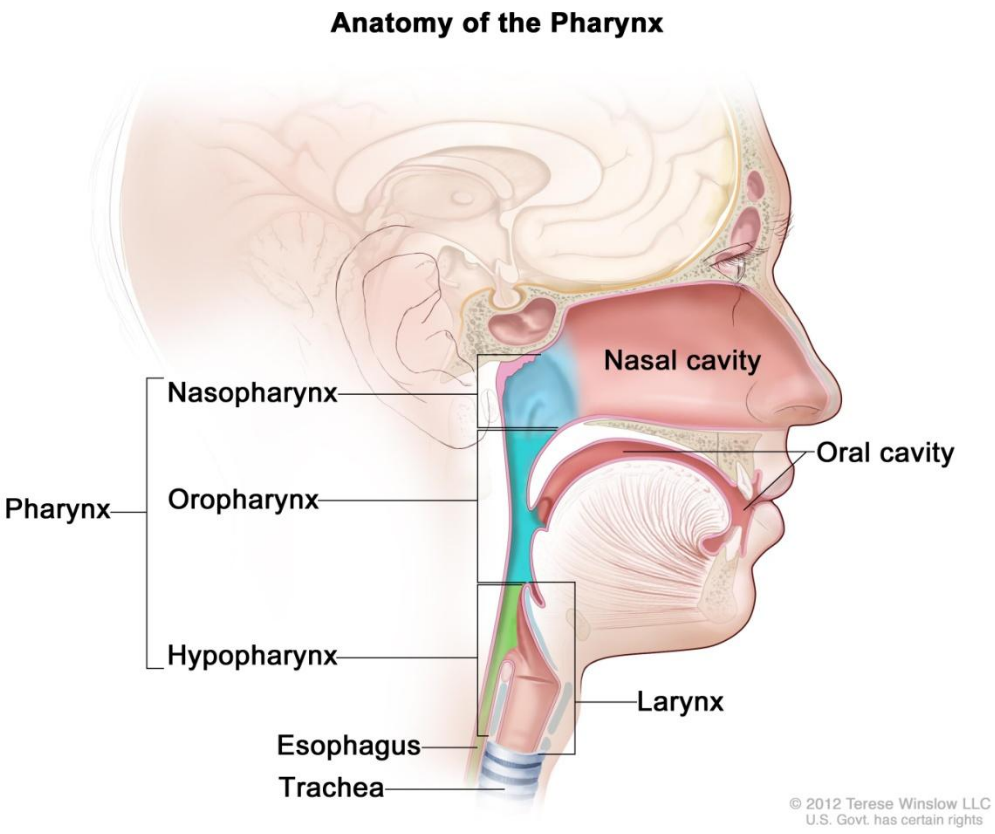


Figure 6: The anatomy of the pharynx

3.2 Tonsillar fossa

Branches of the lingual, facial ascending and internal maxillary arteries supply the tonsillar pillars and fossa with blood. Although the terminal branches of these arteries often have no name, the intermediate branches are worth noting. The ascending pharyngeal artery divides into pharyngeal branch dividing into superior, middle and inferior pharyngeal arteries (14).

The middle and inferior pharyngeal arteries have branches that supply the tonsillar fossa. Additionally, the internal maxillary artery supplies a descending palatine artery that travels through a bony canal into the tonsillar fossa. Usually this artery arises from the ascending palatine and often anastomosis between the internal maxillary and ascending palatine systems exists. The facial artery branches with tonsillar branch and an ascending palatine branch. The ascending palatine artery often branches near the levator veli palatini into a branch that supplies the soft palate and anastomoses with contralateral artery. The other branch penetrates the superior constrictor and supplies the tonsillar fossa. It often anastomoses with both the ascending pharyngeal as well as the tonsillar branch of the facial artery. The venous supply of the tonsillar fossa derives from a plexus of tonsillar veins, which then drains into the retromandibullar vein and eventually into the internal jugular vein.

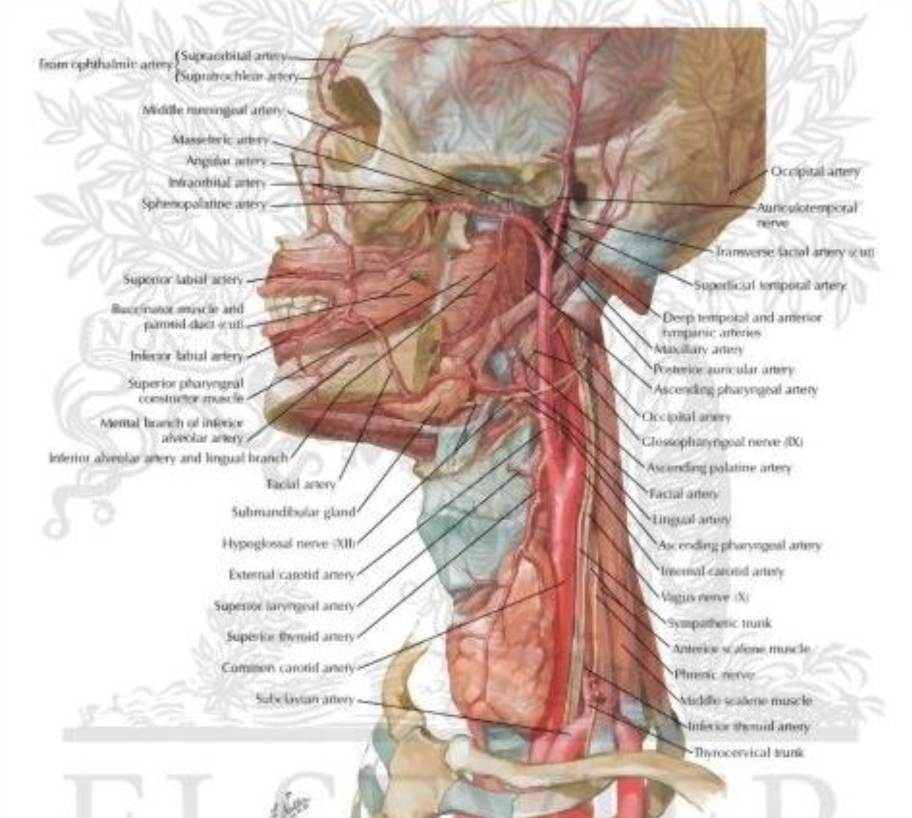


Figure 7: Arteries of Oral and Pharyngeal Regions

The muscle groups can be divided into the constrictors muscles of mastication, palatine muscles and tongue musculature. The medial pterygoid attaches at the medial aspect of the mandible and travels to the medial aspect of the lateral pterygoid plate. This muscle lies just lateral to the superior constrictor. Posteriorly in the oropharynx both the superior and middle constrictors are visible. Laterally the superior constrictor inserts into the pterygomandibular raphe, which is also the lateral border of the tonsillar fossa. The anterior and the posterior tonsillar pillars are defined by the palatoglossus and palatophanygeous muscles respectively. The palatine musculature includes the tensor and levator veli palatini muscles. Lateral to the superior constrictor, the styloglossus, stylohyoid and stylophargeus travel from the styloid process inserting the tongue, hyoid, and thyroid cartilages, respectively.

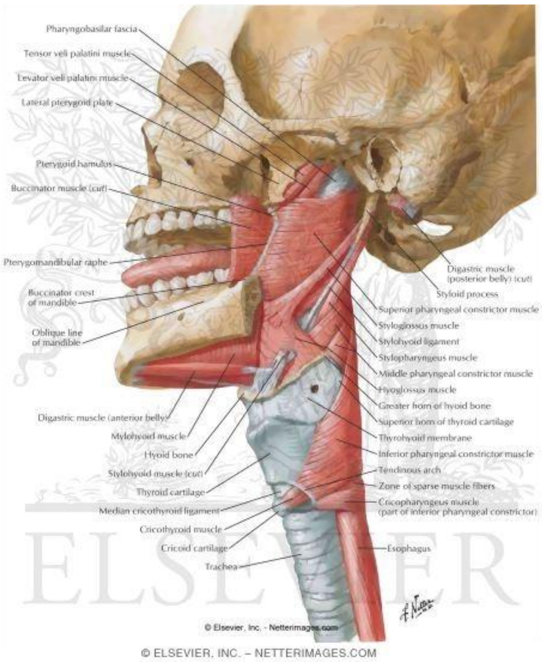


Figure 8: Muscles of Pharynx - Lateral View

When approaching the tonsillar fossa, an incision is soften made through the mucosa and palatoglossus. In radical tonsillectomies, the superior constrictor is medialized, while the ENT surgeon apreciates much of the vasculature after perforating the constrictor and entering the tonsillar fossa (15). As described earlier the ascending pharyngeal artery may be seen supplying the superior pole, whereas the facial artery supplies the midpole as well as the inferior pole alongside wih branches of the lingual artery. Lateral to this plane, the medial pterygoid can be visualized and often the styloglossus lies between the superior constrictor and medial pterygoid. Deep and lateral to the styloglossus by the inferior pole the submandibular gland can be approached intraorally.

Finally, the view that a surgeon can obtain from the robot will be very identical to the view noted when performing a traditional tonsillectomy.

3.3 Base of tongue

The tongue receives its supply from the lingual artery, with the major branch toward the base of tongue (dorsal lingual artery or arteries.arterie). These arteries branch out of the lingual artery and travel superiorly off the main trunk to supply the base of the tongue (Figures 8-9).

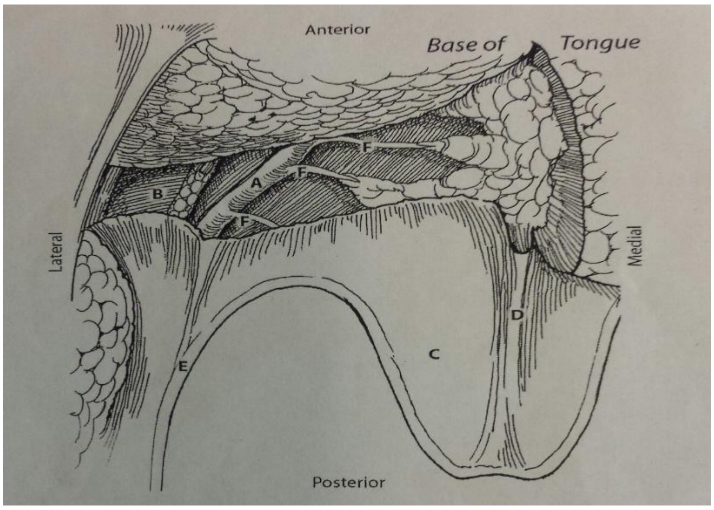


Figure 8: Transoral view of the base of tongue – A.lingual artery, B.hyoglossus muscle, C. Epiglottis, D. Median glossoepiglottic fold and F. Lingual branches of the lingual artery

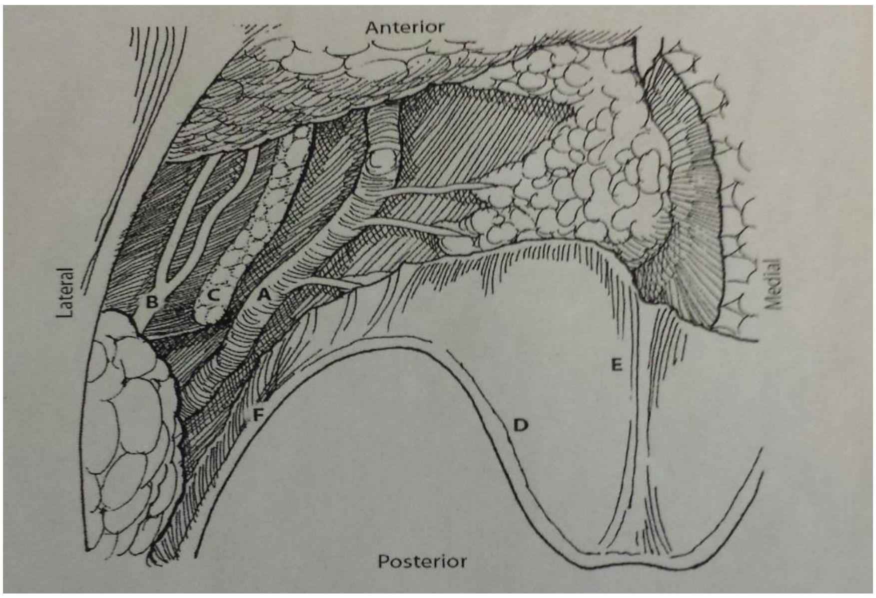


Figure 9: Transoral view of the base of tongue and the lingual nerve - A. Lingual artery B. Lingual nerve C. Hyoglossus myscle D. Epiglottis E.median glossoepiglottic fold and F. Pharyngepiglottic fold.

Associated veins travel with the artery and drain into the internal jugular vein. The tongue consists of both extrinsic and instrinsic muscles. The extrinsic muscles include the styloglossus, palatoglossus and hyoglossus. The genioglossus comprises a significant portion of the body of the tongue and is fixed to the mental spine of the mandible as well as as the hyoid bone and dorsum of the tongue. The hyoglossus lies medial to the stylohyoid and intrudes from the hyoid bone to medial to the styloglossus muscle. The intrinsic muscles constitute thin sheaths of muscle that maintain the shape of the tongue. The base of tongue ends posteriorly at the vallecula and meets the epiglottis. Between the tongue and epiglottis there are the median and lateral glossoepiglottic ligaments, while deep to these structures lies the hyoepiglottic ligament.

If a surgeon wants to approach the base of tongue, then resection of the overlying lymphoid tissue is required. The muscle fibers of the intrinsic muscles are often difficult to define but an extensive vascular network from the dorsal lingual and lingual arteries is easily visualized. The surgeon can often reveal the main trunk of the lingual artery just medial to the insertion of the palatoglossus. The lingual nerve lies lateral to the hyoglossus muscle, whereas the lingual artery is often found medial to this muscle. It is usually easy to identify the hyoid laterally through the nucosa at the level of the vallecula. A branch of the lingual artery can also be identified running toward the lingual surface of the epiglottis.

The hyoid bone can be easily visualized through the mucosa, lateral to the epiglottis at the level of the vallecula. Dissecting through the mucosa would expose the suprahyoid muscular attachments to the hyoid. Dissecting through these muscles to the bone would often reveal the suprahyoid artery. The tendon of the digastric can be found just lateral to the greater cornu of the hyoid bone, alongside the hypoglossal nerve. Deep to the hyoid the thyrohyoid membrane can be visualized by tge surgeon laterally.

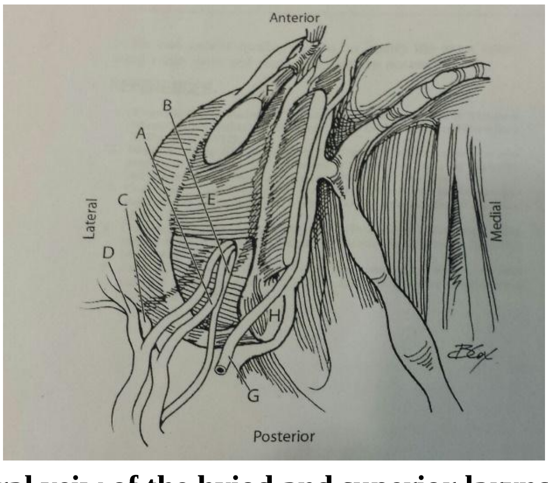


Figure 10. Transoral veiw of the hyiod and superior laryngeal neurovascular bundle A. Superior laryngeal artery B. Laryngeal nerve C superior thyroid artery D superior thyroid vein E. Thyrohyoid muscle F. Tendon of digastric muscle G. Lingual artery H. Greater horn of hyoid bone.

4. STUDY PRESENTATION

4.1 Aim

Aim of this study is a bibliographic review of all emerging applications of TORS in oropharyngeal malignancies.

4.2 Methods

I. Study Selection

For the necessary research, the search engine of Pubmed was used, as well as references from all included studies. Databases were searched until January 2016 using the medical subject headings terms "transoral robotic surgery", "oropharyngeal cancer", "oropharynx and TORS", "unknown primary', "TORS and parapharyngeal space'' and "tongue base" Due to limited publications, and due to the fact that the most of the publications are from the pioneers of TORS and refer to SCC oropharyngeal cancer I divided the search in two columns. I used 2011 reviews only for SCC oropharyngeal cancer and for the other emerging application I used all available publications in order to mention the direction of tors usage in oropharynx. For SCC oropharyngeal cancer I did not use abstracts, case reports, expert opinions, as well as non-English publications. The complete search yielded 27 results. After looking through each publication, I removed two, one of which referred to telesurgery, and the other to benign lesions. The last to be removed was one in which the discussion was in German. The final sum of publications to undergo analysis is shown in Figure 11.

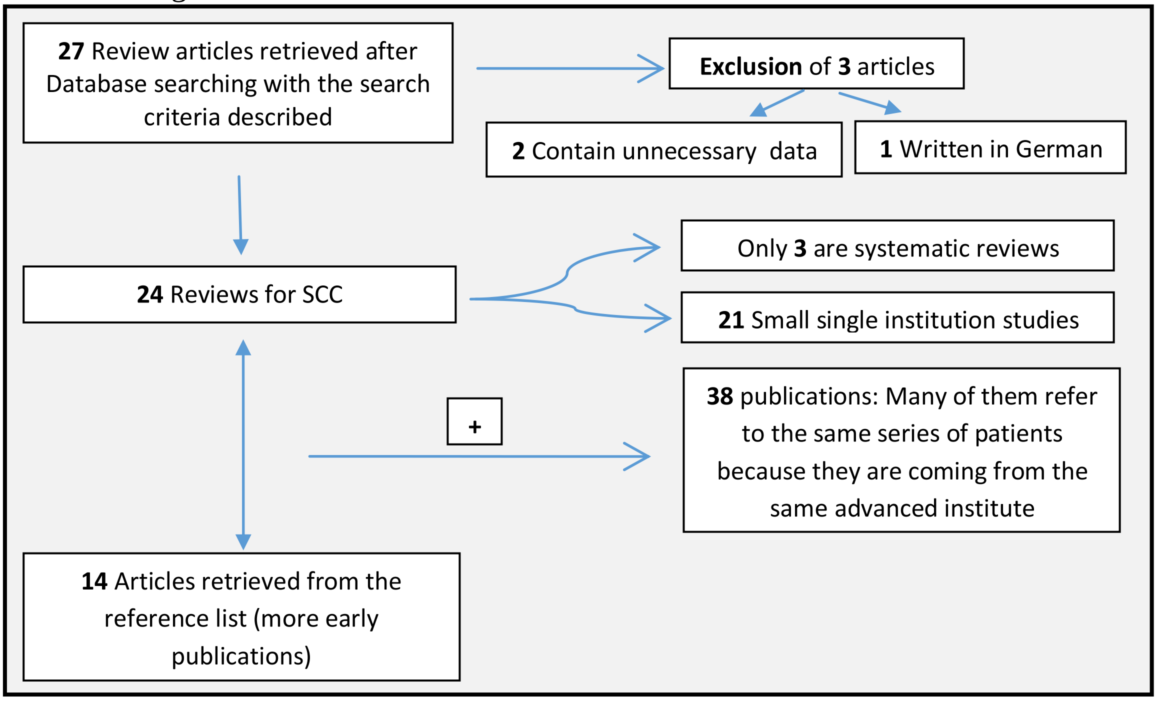


FIGURE 11. Flow chart for the selection process

For the rest of the emerging applications, in order to find more, I conducted my search looking for transoral robotic surgery for the last 5 years only. The complete search yielded 261 results and I excluded those which refer to larynx, nasopharynx and sleep apnoea. The final group of publications to undergo analysis is shown in figure 12.

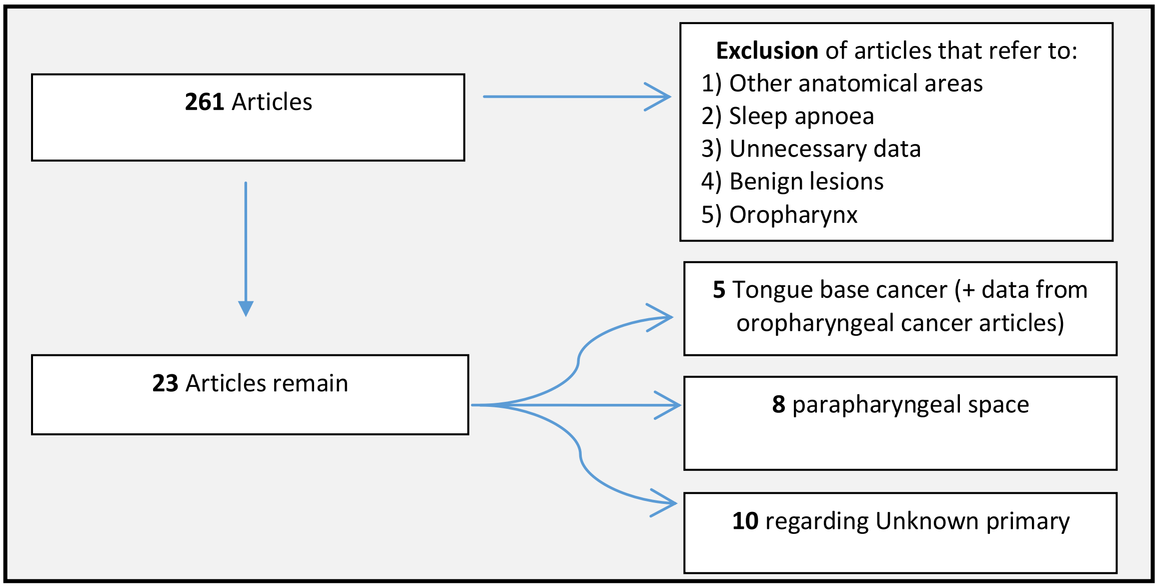


FIGURE 12. Flow chart for the final group of publications to undergo analysis

II. Inclusion and exclusion criteria

The inclusion criteria for eligibility were those who refer to the staging of the cancer, written in the English language. Exclusion criteria were cadaveric studies, as well as studies regarding benign lesions.

III. Outcomes of interest and data extraction

Most of the articles that refer to the outcomes of TORS compare with other optional treatments such as Transoral laser resection, radiotherapy, chemoradiotherapy or open conventional technique.

The following outcomes were used to find out the approved application of TORS and the emerging indication:

1) Indication and number of patient

2) Potential complications

3) Limitation of TORS

4) Comparison of TORS with radiotherapy and conventional technique

A single author (Dr Karamali) abstracted data from each selected article to a structured form. Data abstracted included: first author, year of publication and study population characteristics (including number of patient, staging and two year survival where available). Intraoperative, perioperative and postoperative data, as well as pathologic details were also recorded.

4.3 Results

I. Selection of series

From the articles analyzed there were 36 series of patients who underwent TORS for the different subsites of oropharyngeal cancer as shown in the table that follows. The patient population was 1729 in total.

II. Indications

TORS has generally been approved for T1 and T2 oropharyngeal tumors. However, the recent literature shows comparative results for TORS, when compared with conventional open surgery and transoral laser microsurgery (TLM) for T3 oropharyngeal tumors. For unknown primary cancer on the other hand, TORS seems to have an excellent diagnostic modality of the primary lesion, which may be superior to the procedure of panendoscopy, particularly when treating tumors that are accessed with difficulty or are operated in difficult head and neck regions.

5. DISCUSSION

5.1 HPV and oropharyngeal cancer

As HPV-associated oropharyngeal squamous cell carcinomas (OPSCC) emerged, it was also revealed that they would have considerable prognostic and staging ramifications. Patients afflicted with HPV-related OPSCC usually present with small primary tumours and colossal, often cystic cervical nodes. As a result the staging of these patients in the TNM system is quite high. HPV-positive OPSCC patients are quite likely to present with nodal metastasis and an unknown primary tumor. Particularly, HPV-positive tumor status is correlated with substantially improved rates of survival, treatment modality notwithstanding, when in comparison with HPV-negative tumours (16, 17). OP SCCA is now being stratified into a less intrusive disease or more advancing cancer based on its etiologicy. Ang et al. divided patients undergoing RT for OP SCCA as low risk, intermediate risk, and high risk, related to HPV non-smokers and HPV smokers. Surprisingly, the HPV-positive patients had a 58% lower risk of death (18). The reason for this increasing incidence is and, of course, heterogeneous. There is some data published which proves that HPV-related OP SCCA is more strongly immune controlled. Therefore, many elements of the course of this disease could be explained by this difference, for example its better response to treatment (19), as well as the prolonged time that HPV-mediated OP SCCA patients can live with it before treatment and after the development of distant metastasis.

Patients with HPV positive oropharyngeal cancer have a much better prognosis, compared to HPV negative ones. This fact has given birth to the idea of the de-escalation HPV therapy (20). Nowadays, several studies have proved that patients with smaller, exophytic primary tumours (T1eT2), who proportionally constitute the majority of OP SCCA lesions on presentation, can be satisfactorily treated locally with the use of TORS technique. The ENT surgeon can accurately stage the disease after performing neck dissection, and patients with N0 to N2a neck disease can be treated with surgery alone. On the other hand though, patients with N2b to N3 neck disease would possibly need postoperative adjuvant RT and chemoradiation therapy.

When dealing with younger patients, there is a priori less comorbidity, a better baseline performance status, and longer life expectancies. Therefore, the functional outcomes after management of OPSCC are of even greater priority. The ongoing clinical trials direct their interest at the degradation of the toxicity that is related to treatment and the development of HPV-specific therapies. Thus, the new strategies of treatment contain the use of cetuximab instead of cisplatin for chemoradiation, a dose minimization of radiotherapy and, of course, the new robotic trend of the transoral robotic surgery (TORS). (21)

When an ENT surgeon applies the classic open surgery to his patients, this often involves a lip split, a mandible split, a lateral pharyngotomy or a tongue-dropout technique through the floor of mouth. Of course, this procedure has its significant access-related collateral damages; it leaves cosmetic and functional impairments behind, and has not been a very attractive option so far. As a result, TORS may provide lower morbidity, but equally effective modality, compared to any other surgical treatment, especially for HPV-positive OPSCC patients (22, 23). On the other hand and judging the results from a pure oncological point of view, TORS is a rather safe primary treatment opportunity, since it provides excellent access to the tumor and it does not cause related collateral damage (22, 23).

When we want to decide whether to operate on a specific tumor of a specific patient or not, the ENT surgeon needs to answer three basic questions: (a) Can clear margins be achieved? (b) Can function be preserved? (c) Will the planned surgery reduce the need for adjuvant therapy? TORS has several advantages mentioned so far. The most important of them is the fact that, especially in the region of oropharynx, it makes it far easier and less morbid to achieve 5 mm clear surgical margins around a multi-planar en bloc resection, without demanding floor of mouth release and/ or mandible split. However, irrespective of the treatment modality, adjuvant treatment could be reduced when a surgeon achieves a reliable margin status and when dealing with HPV-driven SCCs, which have better prognosis (24). When we couple the 5 mm clear margin status of the primary tumor with a reliable surgical and pathological staging of the neck (25), a custom tailored adjuvant therapy can be discussed. In this case the ENT surgeon can think of further reducing the additional morbidity to the extent of excluding adjuvant therapy in selected cases (26).

5.2 Current Indications

Transoral robotic surgery (TORS) is a minimally invasive surgical approach that offers surgical access to the oropharynx without the morbidity of open procedures. Meanwhile it is able to achieve excellent oncologic and functional outcomes. Surgeons still investigate the appropriate application of this new technology nowadays, but without any doubt the current literature definitely recognizes TORS as a feasible surgical choice in the management of OPSCC patients.

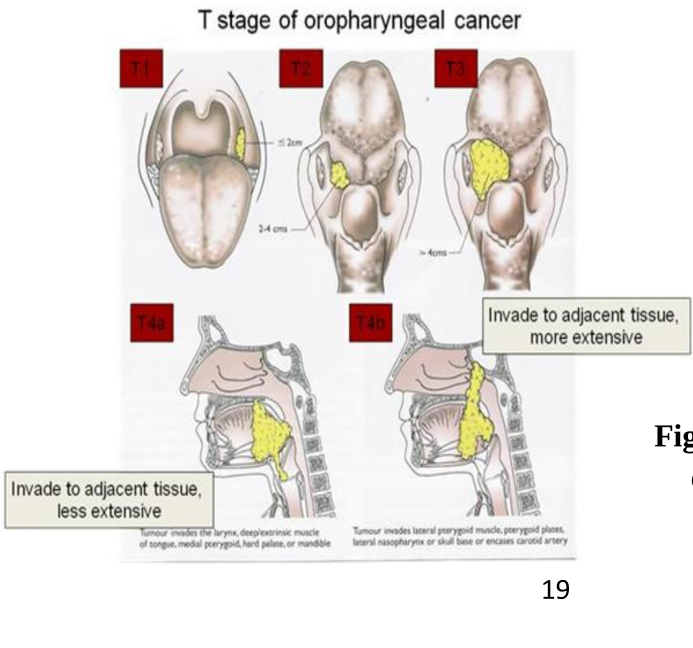


Figure 13: The T staging of oropharyngeal cancer

In the 1970s transoral laser microsurgery (TLM) was first introduced as a surgical technique for laryngeal papillomas. As time passed by, though, it was subsequently used for small laryngeal cancers and more recently for oropharyngeal squamous cell carcinomas (27, 28). Even though good oncological outcomes have been reported, the method of transoral laser microsurgery has been proved to be technically challenging. Therefore, it was largely restricted to specific centres around the world, where significant surgeon expertise exists (28, 29).

On the other hand, ENT surgeons from the University of Pennsylvania first established the feasibility of integrating robotic surgery into the management of head and neck malignancies in 2005 (30, 31). Afterwards, O'Malley, Jr. et al. published the first study of performing TORS for resection of base of the tongue tumours in live patients (32). The authors mentioned first of all the excellent exposure of the tumor, after using the Feyh-Kastenbauer (FK) Retractor and secondly the three-dimensional, high-resolution view of the operative field that the da Vinci Surgical System provided through the 0° and 30° surgical telescopes. These technological advances demonstrated that en bloc resection of OPSCC could be performed safely with the use of TORS and that the challenges associated with TLM could also be faced. Since 2009 TORS has been accepted by the US Food and Drug Administration for being applied in benign and selected malignancies of the head and neck. Ever since, it has undoubtedly become an applicable option in the management of OPSCC patients.

Table 1

Staging for Cancer of the Oropharynx and Oral Cavity (Including the Lip), With 5-Year Survival Rates By Stage

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4	(lip) Tumor invades adjacent structures (eg, through cortical bone, tongue, skin of neck)
T4	(oropharynx and oral cavity) Tumor invades adjacent structures (eg, through cortical bone, soft tissues of neck, deep [extrinsic] muscle of tongue)
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant Metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping		Approximate 5-Year Survival Rate (%)
0	Tis, N0, N0	99%
I	T1, N0, M0	90%-92%
II	T2, N0, M0	75%-85%
III	T3, N0, M0	
	T1, N1, M0	
	T2, N1, M0	50%
	T3, N1, M0	
IV	T4, N0, M0	
	T4, N1, M0	
	Any T, N2, M0	25%-35%
	Any T, N3, M0	
	Any T, Any N, M1	

Adapted with permission from Beahrs OH, Henson DE, Hutter RVP, et al (eds): *Manual for Staging of Cancer*, 4th ed. Chicago, American Joint Committee on Cancer, 1992.

Figure 14: The TNM staging of oropharyngeal and oral cavity cancer

Surgeons should definitely define how TORS should best be applied to the management of OPSCC patients. It is well established so far that TORS is applicable to early stage OPSCC (T1-2, N0-1), as RT might be avoided (33). The utility of TORS is diminished. In patients with high tumour (T) classification or with large volume, surgeons cannot really apply TORS because they are not able to obtain negative surgical margins and the functional morbidity is increased anyway. On the other hand, advanced stage tumors can also be managed with a combination of TORS and other adjuvant therapies. Thus, potential late toxicities are avoided (34). Specifically, it has been found that when we decrease the dose of RT from 66–70 Gy to a post-operative dose of 54–60 Gy we are able to lower the risk of severe long term toxicities, among which osteoradionecrosis of the jaw is included. If we want to obtain the most accurate information for the staging of the cancer and therefore to apply more tailored adjuvant therapies, the surgical treatment of the disease is essential. In an initial study published in 2010, 47 patients with stage III or IV OPSCC were treated with TORS, staged neck dissection, and adjuvant therapies as indicated (35). In this particular study, authors first investigated TORS for the management of advanced-stage OPSCC.

Authors defined as the indications for adjuvant chemotherapy the positive surgical margins and the extracapsular spread of the tumor. Overall, oncologic outcomes were similar to published CRT studies and 38 % of the patients managed to avoid chemoratiotherapy. In the same year, Boudreaux et al. (36) published a prospective non-randomized clinical trial which included T1–T4 tumours of the upper aerodigestive tract. All these were managed surgically with TORS. In this study the authors showed that it was achievable to obtain negative margins with excellent functional results even for advanced tumors. The patients who were incapable, though, of undergoing TORS were only six, basically because of technical difficulties or inadequate exposure of the mass.

In another study by Kucur et al (37) 73 patients with early oropharyngeal cancer were analyzed. The authors tried to investigate how often the parapharyneal space (PPS) was invaded in the cases studied. As expected, when structures like the carotid artery, the internal jugular vein and the cranial nerves IX-XII were invaded, the morbidity was significantly influenced. The preoperative evaluation included a detailed physical and endoscopic examination, neck CT and/or PET-CT scan, elements that defined the selection of patients. Finally patients with T1, T2 and selected T3 tumors and no obvious PPS extension on preoperative evaluation were included in the study. All patients had OPSCC in palatine tonsil (60; 82.2 %) and base of tongue (13; 17.8 %). In clinical and radiologic evaluation 27 patients had cT1 (37%), 39 had cT2 (53.4 %), and 7 had cT3 (9.6 %) disease. All patients underwent TORS radical tonsillectomy or TORS base of tongue resection with neck dissection. During TORS procedure, PPS was encountered in 18 (24.6 %) patients after the resection of the deep margin. With the exception of 3 patients, the authors managed to remove the lesions en bloc with negative surgical margins in the great majority of them. The resection of oropharyngeal cancer extending to PPS appears to be a feasible and safe technique with only a few complications. Of course, as long as surgeons gain experience with TORS and further understand the endoscopic anatomy of PPS, the morbidity that is associated with tumor resection in this neurovascular region can be significantly reduced.

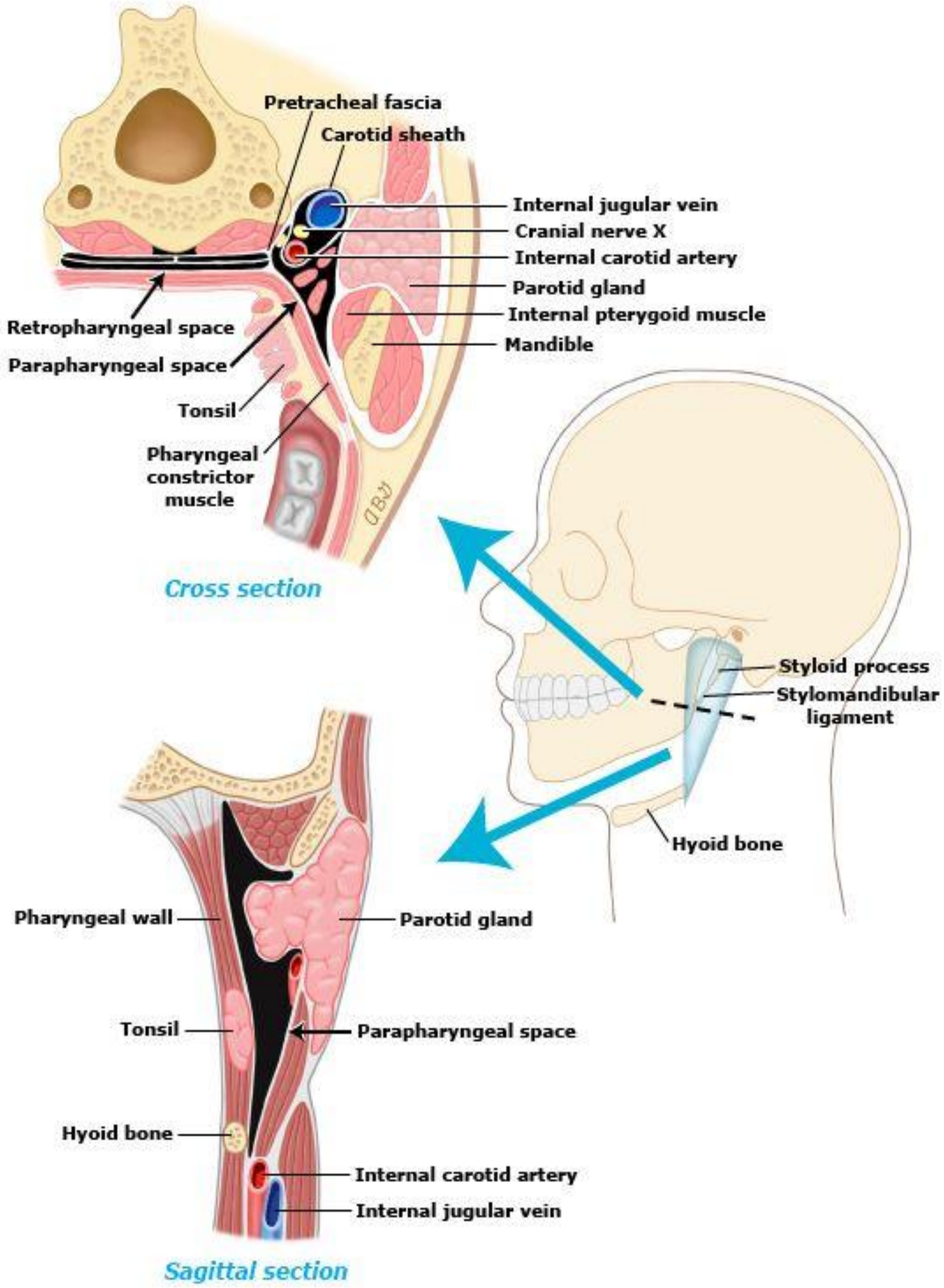


Figure 15: The parapharyngeal space anatomy

5.3 Limitations / Containdications of TORS for oropharyngeal cancer

The contraindications of TORS are listed in a study from the pioneers in Transoral Robotic Surgery (TORS) (38). These are:

- **Vascular** contraindications of TORS for oropharyngeal cancer:

1. Tonsillar cancer with a retropharyngeal carotid artery
2. Epicentric of the tumor is in the midline of tongue base or vallecullae which would put both lingual arteries at risk
3. Tumor adjacent to carotid bulb or internal carotid artery which will result in intraoperative exposure if the vessel.
4. Encasement of the carotid artery by the primary tumor T4b or by a metastatic neck node

- **Functional** contraindications of TORS for oropharyngeal cancer:

1. Tumor resection requiring more than 50% of the deep tongue base musculature
2. Tumor resection requiring more than 50% of the posterior pharyngeal wall
3. Tumor resection requiring up to 50% of the tongue base as well as the entire epiglottis

- **Oncologic** contraindications of TORS for oropharyngeal cancer:

1. All T4b cancers
2. Posterolateral fixation of tonsillar cancers to the prevertebral fascia. This is assessed by utilizing bimanual palpation with one finger placed intraorally and the opposite hand palpating extraorally. Fixation can be assessed by gently rocking the soft tissue of the tonsillar fossa medially and laterally.
3. Unresectable neck disease.
4. Neoplastic related trismus
5. Multiple distant metastases

On the one hand, the tumor-related indications for oropharyngeal TORS resection include the previously untreated biopsy-proved squamous cell carcinomas of the oropharynx (ie, American Joint Committee on Cancer [AJCC] stages III, IVA, and IVB, including AJCC TNM T1, T2, T3, and T4a cancers). On the other hand, the **tumor-related** contraindications for TORS resection of AOC include:

1. Stage IVC, except for a curable distant metastasis

2. Unresectability of the involved lymph nodes

3. AJCC TNM T4a, except for the unilateral deep/extrinsic muscle of the tongue

4. Tumor-related trismus

5. AJCC TNM T4b

6. Any AJCC T category with invasion of the deep tissues lateral to the constrictor muscles or posterior invasion of the prevertebral fascia.

The ENT surgeon should always confirm this lateral and deep invasion of the tumor as fixation laterally or posteriorly by palpation, and should not just rely on the radiological findings. Consequently, the cervical nodes are regarded as unresectable when the carotid artery is encased within the deep neck structures. This often results in the prediction that the nodes cannot be grossly resected. On the other hand, when advanced oropharyngeal cancer is diagnosed, there is also skin invasion with dermal metastasis.

Non-oncologic contraindications of TORS for oropharyngeal cancer include:

1. A medical condition that precludes stopping antiplatelet medications or anticoagulations
2. As with all surgical approaches, any systemic or degenerative disease which is associated with unacceptable morbitity or mortality during general anesthesia or during the postoperative period
3. Non-cancer related trismus, which prevents robotic access via the oral cavity
4. Cervical spine disease that interferes with necessary patient positioning during TORS.

Even though the transoral robotic approach has been applied in many regions of head and neck nowadays, it still has a lot of limitations, as well as risks while being performed. Thus, in order to enlarge local control, to improve functional outcome and to avoid vascular injury, several indications and contraindications are determined. First of all, all the indications and contraindications should be thoroughly taken into consideration. Secondly the choice of the appropriate patient is crucial, so as the surgeon will not experience severe complications or the possibility to switch the approach from robotic to open procedure and to order en bloc resections. Last but not least, the surgeon should be experienced and adequately trained on transoral robotic, as well as traditional open surgical approaches.

5.4 Changes in the management of oropharyngeal cancer

Standard treatment for patients ten years ago was surgery, in some cases including Radiation Therapy (RT) or neck dissection (39). These patients, in their majority, were dependent on either open surgical resection with mandibulotomy, complete (radical) neck dissection during their primary surgical therapy or after their primary non-surgical therapy, and external beam RT without Intensity Modulated RT (IMRT). These modalities were the therapeutical standards by that time. A history of intense alcohol and tobacco use was present in most patients, since that was the most commonplace risk factor for OP SCCA for the span of this three-decade period. The amassed 5-year survival in these studies was 47% for the patients that underwent surgery, either with or without RT, and 43% for patients subjected to RT, even if they treated surgically with neck dissection or not. After observing that the severe complication rate stood at 23% in the primary surgery group, and at 6% in the primary RT group, the authors reached the conclusion that it would be more desirable to employ non-operative therapy rather than operative therapy regarding OP SCCA, whatever its stage. As it was made evident by Chen et al., primary chemoradiation therapy (CRT) for OP SCCA at all institutions in the United States reached a double peak between 1985 and 2001, while both primary surgical therapy and primary RT were employed at a declining regularity(40).

During that time, technology kept changing as it progressed, and the nature of the disease was shifting in many ways as well. To begin with, the disease that was initially a relatively unusual tumor affecting primarily alcohol- and tobacco-abusing old men was transforming into an increasingly common cancer mediated by a sexually transmitted human papilloma virus (predominantly HPV 16) that a lot of healthy adults were at least exposed to at a younger age. As a result, the consequences of said metamorphosis are extensive, not only for the population at risk that is alerted to the cancer, but also the behavior of the cancer and outcomes of treatment. Secondly, the delivery of operative and non-operative therapy has been changed due to the influence of technology. Distribution of radiation along with computerized planning were altering the course of treatment and most surgeons would argue whether this could alter the morbidity associated with RT (41).

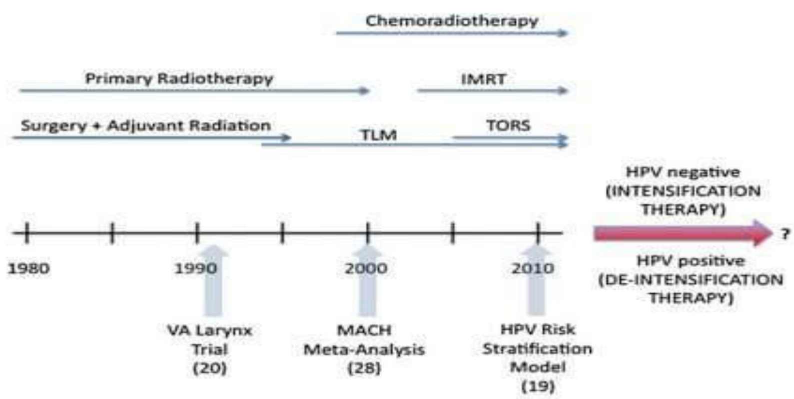


Figure 16: Changes in the management of oropharyngeal cancer and important stages of its diagnostic and therapeutic evolution

Neck dissection was becoming more selective in surgery, and head-and-neck surgeons discovered that they could accomplish the same objectives of pathologic staging and therapeutic neck metastasis removal without removing the "normal" neurovascular structures which were resected with a typical "radical" neck dissection. Furthermore, a few chosen centres were using procedures perfected in laser laryngoscopy to remove tumours in other head-and-neck sites through the oral cavity. In this way, the number of "open" resections, mandibulotomies and pharyngotomies that were performed declined. To conclude, the use of robotic instruments and the progress of technology in endoscopes resulted in the Da Vinci surgical robot (Intuitive

Surgical, Sunnyvale, CA). It was employed in head-and-neck surgery to carry out transoral resection with two-handed dexterity.

Consequently, the use of robotic techniques improved the loco-regional control of the tumor, as well as the primary surgical excision of the tumor, instead of RT. It is worthy of note that the latter hinges on the experience of each center. There is an article published, where authors tried to find out all the published indications of TORS for oropharyngeal cancer, for example in which region of the oropharynx and for which size of lesion (42).

5.4.1 Oncologic Outcomes

Scoping literature, we could draw the conclusion that the first published data regarding oncologic outcomes of TORS for OPSCC are encouraging. Undoubtedly, patients treated with TORS have a much better evolution, when compared to patients treated with traditional open surgical approaches. Ford et al. at the University of Alabama Birmingham retrospectively reviewed 130 cases of primary OPSCC (43). Sixty-five patients were included in each group and were treated with either TORS or open surgery plus standard of care adjuvant therapy (44). As a group, those treated with TORS had improved survival at 1, 2, and 3 years (94, 91, 89 %, respectively) when compared to stage-matched patients treated with open surgery (85, 75, 73 %, correspondingly). Compared with CRT for the management of advanced OPSCC, TORS has also shown superiority in several fields. Authors reported excellent disease-free survival at 1 year (96 %) and 2 years (79 %) in 47 patients with stage III or IV OPSCC treated with TORS (45). Since then, several groups have published similarly encouraging disease-specific and recurrence-free survival data. Nonetheless some studies included multiple anatomical regions of the head and neck and few calculated the same outcome measures. Moreover, the authors reported similar oncologic results to those achieved with intensity-modulated radiation therapy (IMRT)-based CRT (46, 47). In order to eradicate the oncologic impact of TORS in OPSCC, Weinstein et al. studied 30 previously untreated OPSCC patients (stages I–IV) who underwent TORS without adjuvant therapy and published their outcomes (48). The authors defined the negative margins as >2 mm and a minimum follow- up of 18 months (mean 27 months).Thus, local, regional, and distant disease control was achieved in 29 of 30 (97 %), 27 of 30 (90 %), and 30 of 30 (100 %) cases, respectively. The investigators concluded, after all, that in selected patients with favourable pathologic features TORS alone offers excellent local control at the primary site. In another study by Kelly et al. (49) a systematic review of oncologic and functional outcomes after primary TORS for T1-2 OPC was carried out. These authors reported total local, regional, and distant control rates of 96.2, 91, and 100%, respectively. However, all of the 11 selected TORS studies had 4 to 42 patients (namely small sample sizes) and short follow-up (median 19.9 months). The oncologic and functional outcomes should be re-estimated in future studies though, especially in HPV-positive patients who tend to manifest distant metastasis of late onset (50).

5.4.2 Functional outcomes

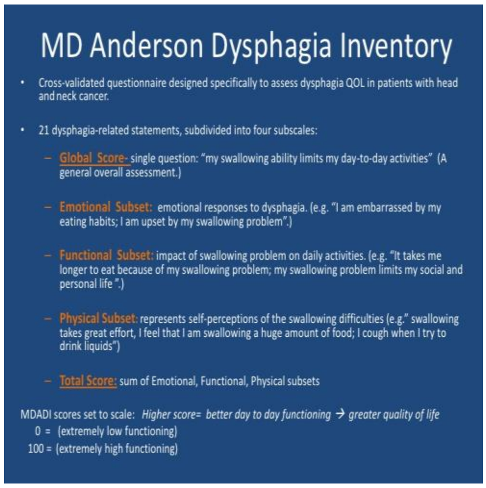
Every time we compare TORS to traditional surgical approaches for OPSCC, the superiority of TORS regarding improved functional outcomes is more than obvious. In several early studies the continued use of tracheostomy and gastrostomy tube was used as a marker of functional preservation (51-53). The long-term dependence of gastrostomy tube ranged from 2.4 to 16.7 %, whereas the higher the retention rates were, the higher the tumour stage was. Alternatively, it was more possible for the tumor to be recurrence or second primary. However, as experience increased, tracheostomy and gastrostomy tube retention rates have improved and nowadays range from 0 to 2 and 2 to 9 %, respectively. In comparison, several studies report that the rates of gastrostomy tube dependence are around 15 to 25 % after primary RT for OPSCC and increase to 18.1 to 51 % following CRT (54). As time passes by, authors tend to use more precise outcomes measures to assess functional outcomes. There is, for instance, a validated self-administered questionnaire, the M.D. Anderson Dysphagia Inventory (MDADI), that can be used for the evaluation of the impact of dysphagia on the QOL in patients with head and neck cancer (55). This questionnaire has been used in several studies, in order to assess swallow function of the patients over time (56). Generally speaking, the mean Dysphagia Inventory scores tend to drop from baseline in all domains postoperatively (global, emotional, physical, and functional). Even if there could be a slight increase in some post-operative subscale scores, the overall scores are much better, compared to those published in other studies evaluating the MDADI in OPSCC patients treated with CRT (57). More et al. compared the MDADI between patients with advanced stage OPSCC and supraglottic cancer who followed either TORS or CRT, in a prospective non-randomized trial (58). As a result they found that 3 months after the treatment there was no difference in the mean MDADI scores between the groups, but that there was a difference at 6 months and 1 year. The TORS group had a significantly better mean MDADI score at 6 months and returned to baseline (=78) at 1 year, whereas the CRT group fell from a baseline of 78 but only recovered to a mean score of 60. As expected by the aythors, the higher the tumor classification was, the worse the MDADI scores in both treatment groups. Dziegielewski et al. (59) used another validated, quantitative QOL instrument, the Head and Neck Cancer Inventory, so as to assess the QOL in the fields of speech, eating, aesthetics, and social disruption. Three weeks after surgery, there was an expected drop in all health-related QOL (HRQOL) domains. Scores kept declining and the worst moment was noted 3 months postoperatively. At that time, there was a coincidence with RT and/or CRT. Values though, increased again 12 months post-op. One year post-op, the HRQOL domains that were influenced the most were the eating function and attitude. Particularly, the lowest eating HRQOL domain scores were noted in patients who required adjuvant therapy. Nevertheless, no statistical differences were noticed between patients who received either CRT or adjuvant RT. These findings are compatible with the study of Levendag et al. (60), as the latter realized that the higher doses of radiation have an elevated possibility of swallowing dysfunction and that, finally, RT plays the most important role to post-treatment dysphagia, compared to that of chemotherapy.


Appendix 1. The MD Anderson dysphagia inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.
The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.
Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.
Strongly Agree Agree No opinion Disagree Strongly Disagree
E2. I am embarrassed by my eating habits.
Strongly Agree Agree No opinion Disagree Strongly Disagree
F1. People have difficulty cooking for me.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P2. Swallowing is more difficult at the end of the day.
Strongly Agree Agree No opinion Disagree Strongly Disagree
E7. I do not feel self-conscious when I eat.
Strongly Agree Agree No opinion Disagree Strongly Disagree
E4. I am upset by my swallowing problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P6. Swallowing takes great effort.
Strongly Agree Agree No opinion Disagree Strongly Disagree
E5. I do not go out because of my swallowing problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
F5. My swallowing difficulty has caused me to lose income.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P7. It takes me longer to eat because of my swallowing problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P3. People ask me, "Why can't you eat that?"
Strongly Agree Agree No opinion Disagree Strongly Disagree
E3. Other people are irritated by my eating problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P8. I cough when I try to drink liquids.
Strongly Agree Agree No opinion Disagree Strongly Disagree
F3. My swallowing problems limit my social and personal life.
Strongly Agree Agree No opinion Disagree Strongly Disagree
F2. I feel free to go out to eat with my friends, neighbors, and relatives
Strongly Agree Agree No opinion Disagree Strongly Disagree
P5. I limit my food intake because of my swallowing difficulty.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P1. I cannot maintain my weight because of my swallowing problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
E6. I have low self-esteem because of my swallowing problem.
Strongly Agree Agree No opinion Disagree Strongly Disagree
P4. I feel that I am swallowing a huge amount of food.
Strongly Agree Agree No opinion Disagree Strongly Disagree
F4. I feel excluded because of my eating habits.
Strongly Agree Agree No opinion Disagree Strongly Disagree

Thank you for completing this questionnaire!



Figures 17-18: The M. D. Anderson Dysphagia Inventory.

If we compare TORS with the traditional open surgical approaches, the first technique has several advantages over the latter. These include: improved postoperative recovery (including hospital stay and swallowing recovery), a significantly higher rate of negative margins and shorter operative time in patients with T1 to T3 tonsillar squamous cell carcinoma.

Lee et al (61) published another study, where they examined matched cohorts of patients with T1 to T3 disease undergoing transoral lateral oropharyngectomy. The first group included 27 patients, where TORS was applied. The other group was compromised of patients treated with conventional surgery through a transoral approach or mandibulotomy approach to allow for radical tonsillectomy (30 patients, of whom 14 underwent the mandibulotomy approach). Although the population of the study was limited, more positive margins were detected in the conventional transoral surgery group and mandibulotomy group, compared with the TORS cohort. Between the two groups, the overall 2-year survival and disease-free survival rates did not differ significantly. Undoubtedly, taking into consideration the parameters of duration of hospital stay, return to oral diet, and time to tracheostomy decannulation, the mandibulotomy approach was by far the worst, when it was compared with the transoral approaches.

As a result, surgeons tend to choose less invasive approaches like TORS, as they seem to be superior to open approaches in selected patients. White et al (62) compared TORS with standard open approaches for salvage surgery in patients with recurrent oropharynx cancer. In their study it was found that TORS was less morbid, with reduced blood loss, reduced postoperative infection rate, reduced number of feeding tube placements, shorter duration of hospital stay, reduced positive margins, but similar amounts of airway edema.

In a retrospective study by Samuel et al. patients, who were treated with transoral robotic surgery, survived more frequently (94%, 91%, 89% at 1, 2, 3 years, respectively) than the patients treated with open surgery (85%, 75%, 73% at 1, 2, 3 years, correspondingly). On the other hand, patients compromising the subgroup with HPV negative malignancies treated with open surgery survived without recurrence less frequently at 1, 2, and 3 year rates of 58%, 25%, 25%, respectively. From the data mentioned above, it is suggested that surgeons do not yield the oncologic outcomes when they treat patients with OPSCC with TORS instead of open surgery, regardless of the immuno-histochemical staining of the HPV tumor.

5.5 Comparison of TORS with TOLM

There are several disadvantages associated with the TLM technique: a restricted field of vision, the need for a TLM-trained pathologist and an additional consumption of operative time, because of the multiple intraoperative frozen sections that need to be taken. These specimens could be taken in pieces, as the resection may require intentional incision through the tumour, so that the surgeon can visually reach the depth of the tumour. In addition to that, TLM relies on the skills and experience of the surgeon to a great extend. Lee et al (63) described in their cohort of patients the challenges and difficulties of gaining an optimal intraoperative view of undergoing radial tonsillectomy. These difficulties are connected with the challenge of physically maneuvering the tumour to obtain a better operative view. Compared with the traditional transoral approaches, the surgical robot is able to provide superior maneuverability and excellent visualization. Its binocular cameras, wristed instruments and tremor reduction system contribute greatly to the view and stability provided (64, 65). As a matter of fact, Vicini et al. (66) stressed out the great advantage of a TORS surgeon to be able to locate and work in areas that could not be reached or seen using the TLM approach. Moreover, the da Vinci robotic system is capable of manipulating tissues gently and providing excellent control while performing restricted motions (67, 68).

Lastly, Ansarin et al. (69) compared TORS to TLM, after studying the first 10 patients of each group in their own institution. Transoral robotic surgery was associated with the well known pros already mentioned before: decreased operative time, greater subjective comfort for the surgeon and longer disease-free survival.

Surprisingly though, it resulted in higher rates of positive margins, maybe because of the thermal injury caused. Of course, additional experience might decrease these rates in the near future.

5.6 Complications

Scoping literature, TORS has been proved to be a safe technique compared to traditional open surgical approaches. In a multi-centre study where 177 TORS cases were reviewed, no intraoperative or perioperative fatalities were mentioned (70). No instances of wound dehiscence, fistulas, or carotid artery injuries were recorded, although 16% of the patients had a serious complication (e.g., pneumonia, myocardial infarction) that required readmission or intervention. Reviewing 1534 non-robotic OPSCC surgeries between 1990 and 2009, there is a wound complication rate of 7.4 % and an in-hospital death rate of 1.0 % (71). The worst complication after TORS is the postoperative bleeding and, of course, the reported rates are not insignificant. Otherwise, the inability to deal with the hemorrhage fast might be proved fatal. In a retrospective survey of 2015 TORS cases in the USA the complication rate was 10%, while the postoperative hemorrhage was the most common complication at a rate of 3%(72). In the study of Asher et al., a hemorrhage rate of 7.5 % has been reported. Among these patients, 9 out of 11 required to be returned to the OR after TORS for their bleeding to be controlled (73). However, 72 % of these patients had commenced antithrombotic drugs for other medical comorbidities. Other studies report similar rates of post-operative hemorrhage (6.3–7.3 %) after transoral surgery via TLM or TORS (70, 74). Impressively, in the study of Pollei et al. (74) at post-operative days 7–14 the bleeding risk was greatest. In addition to that, the authors also concluded that the higher the cancer staging was, the more likely was it to bleed severely. Even though no differences were noted in bleeding rate with transcervical vessel ligation at the time of initial surgery, less severe bleeds were noticed in patients who did.

5.7 Other emerging applications

5.7.1 Base of tongue

The base of the tongue is anatomically defined as the region of the tongue posterior to the circumvallate papillae that includes the vallecula as well. The base of tongue is composed of a blanket of lymphoid tissue similar to the tonsils and consequently this tissue may give rise to several malignancies, like lymphomas in addition to squamous cell carcinomas (75).When an ENT specialist treats a tongue base cancer, then a combination of Radiation therapy (RT) and chemotherapy (CHT) or by gross open surgical approach like a trans-mandibular conservative approach with mandibuloty and paryngectomy or a transpharyngeal approach. If we scope literature, we will find out that there are several centers around the world where the early stage of tongue base cancers (T1 and T2) are operated with Transoral Robotic Surgery (TORS). Furthermore there is a study published by O'Malley et al. (76), where series of advanced tongue base cancer were operated by TORS. As a result, the open procedure was avoided and the opportunity of decreased dose of RT was offered postoperatively.

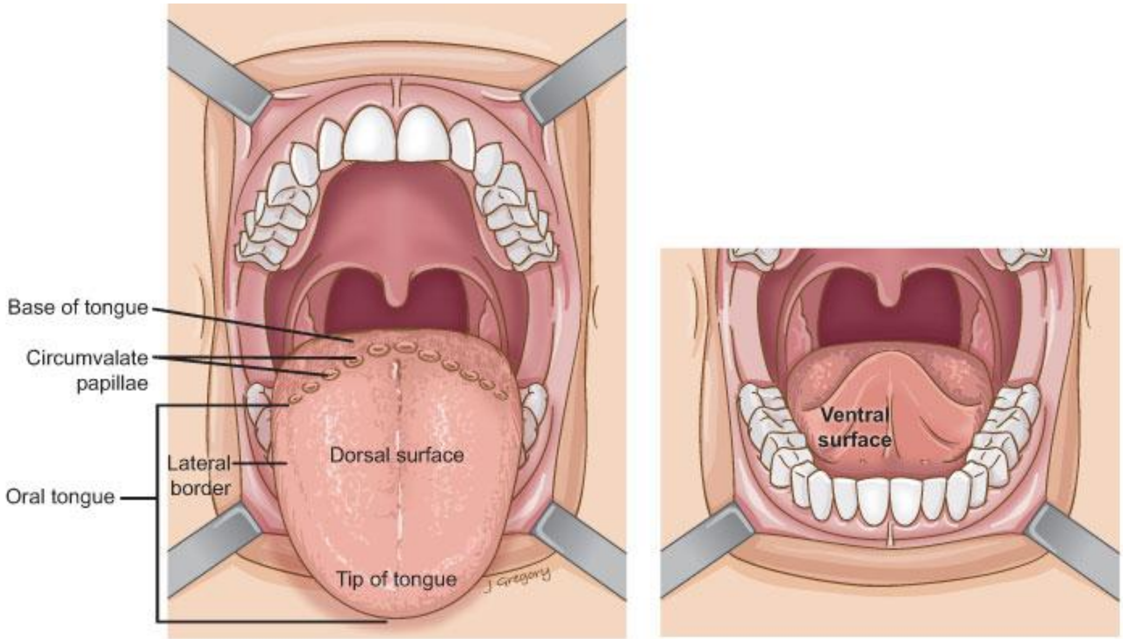


Figure 19: The anatomy of the tongue

The Da Vinci Surgical Robot System provides excellent visualization of the surgical field and, regarding the base of the tongue in particular, enables the removal of the posterior one third to one half of it in cadavers, dogs, and, of course, human beings. Among the three retractors used during the procedure, the FK retractor generally offers the greatest overall exposure, excellent versatility and fine robotic instrument maneuverability. As a result, the ENT surgeon is able to achieve complete resection to negative surgical margins with excellent hemostasis and no significant complications in the live patient surgeries.

Undoubtedly TORS offers great surgical advantages. However, he base of tongue remains a difficult anatomical region for a surgeon to access even with TORS. In a study from Adam Luginbuhl et al. (77) 31 patients had cephalometric measurements done on preoperative imaging, as authors wanted to estimate the predicting parameters for TORS access. Within this study, three evaluations were found to be significantly different between the two groups, these with adequate exposure and those with restricted exposure. The measurements which were all statistically different between the two groups were: the distances from Posterior Pharyngeal Wall (PPW) to hyoid, PPW to soft palate and epiglottis to vertical laryngeal angle. Receiver operating characteristic (ROC) analysis showed a strong correlation to exposure for all three measurements with cut offs B30 mm between the PPW and the hyoid, B8.1 mm PPW and soft palate and C130 between the epiglottis and vertical plain of the larynx, all indicating restricted exposure. Authors believe that these values could predict which patients would gain from an endoscopy for staging purposes, in order to determine acceptable TORS exposure, as well.

There are two surgical techniques: complete en bloc tumor resection for each tumor versus the piecemeal or cutting through tumor resection mandated by the transoral laser surgery procedure. After the application of TORS for the tongue base resection, neck dissections are completed as an independent procedure in order to avoid a mistaken entrance into the pharynx at the time of robotic resection. When a surgeon wants to access the tongue base in human patients, either the Crowe Davis or FK retractor is used. The fundamental outcomes in this TORS study were instrument access to the tumor and exposure which would allow a complete tumor resection to be achieved. Accessory endpoints were times for set-up and safety. In each patient, both the Crowe Davis and FK retractors were used to justify which one of them provided the best exposure of the surgical field. On the one hand, the Crowe Davis provided feasible access to the base of the tongue. On the other hand, though the vallecular blade of the FK with three-directional adjustment capability and the connection of cheek retractors provided the most flexibility in order to achieve ideal exposure. Therefore, between the two retractors, the FK one was actually used to perform the surgical procedures.

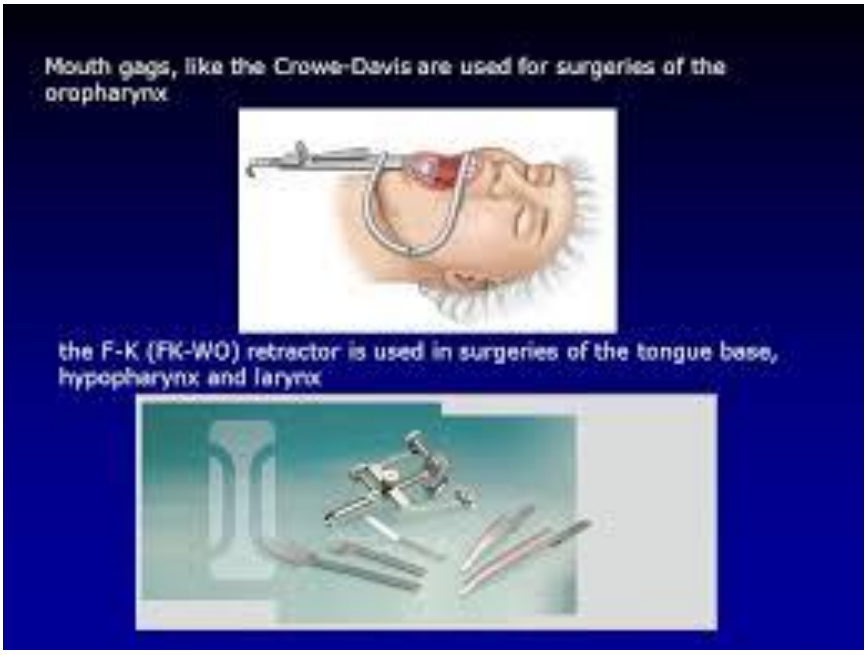


Figure 20: The Crowe Davis and the FK retractor

The method of transoral laser microsurgery has also been applied for the treatment of tongue lesions. Nonetheless it is technically demanding and challenging, and has a long learning curve , as well as a limited surgical field of view as a laryngoscope is used for its execution. Furthermore, the transoral laser surgery requires direct incision through the tumor to justify the extent of resection (78). Probably the lack of widespread appeal of this approach is associated with these limitations. However, 92% of patients achieved swallowing without permanent gastrostomy tube with the transoral approach (79). Taking into consideration these excellent swallowing function results and ignoring some of the disadvantages of endoscopic laser surgery outlined above, we could assume that TORS should yield similar functional outcomes when treating tongue base neoplasms.

Figure 21: The method of transoral laser microsurgery

It has been over a decade that the use of primary radiation or combined chemotherapy and radiation for tongue base neoplasms has been increased (80). These treatments, though, have several complications like various levels of significant swallowing and speech dysfunction, as well as cosmetic deformities, varying degrees of chronic pain and xerostomia (81). As regards survival though, it may be better with surgery plus radiation when compared with either radiation alone or combined chemoradiation (82), based on a gross retrospective analysis of a large number of patients in the National Cancer Data Base.

It is well established so far that TORS for tongue base lesions has significant advantages over both classical open tongue base surgery and laser microsurgery. In comparison with open surgical techniques, it is widely reported that open surgery of the tongue base has obvious negative effects on both cosmetic and functional outcomes. On the other hand, TORS reduces the need for mandibulotomy with a lip split or visor flap or transpharyngeal approaches. All these approaches otherwise affect the important human functions of mastication, swallowing and speech, along with cosmesis. Furthermore, open approaches have a known risk of infections and fistula formation, as an artificial communication is created between the oral cavity and the neck. Moreover, the tracheostomy is avoided when performing tongue base resections with TORS, whereas the open approaches cannot be performed safely without it.

Marcante G. Et al. from Italy (83) published a prospective study, where they evaluated the quality of life (QoL) one year after the patients were treated with TORS as monotherapy. Their study included 13 patients with base of the tongue (BOS) tumors, stages T1 and T2. Data extraction was in favor of TORS, although objective swallowing deterioration in the first 6 months after TORS alone for BOT tumors was probable. Surprisingly, complete recovery of deglutition was observed within 12 months. Patients reported no changes reported in the self-perceived status of swallowing and voice dysfunction, and related QoL 1 year post-operatively.

From the points mentioned above, we can easily draw a conclusion that TORS offers access to the tongue base, an anatomical area which was unable to be reached before without an open approach, and provides a good quality for the patient without sacrificing the oncological standards for the resection.

5.7.2 The retropharyngeal space

In patients with OPSCC, retropharyngeal lymph node TORS has also been employed in order to perform retropharyngeal lymph node dissections (RPLN). In approximately 10-16% of OPSCC patients, there is a radiographic involvement of the RPLN, fact that is basically associated with more advanced disease. Therefore, it suggests a worse prognosis a priori (84). A few years ago, Byeon et al. (85) reported on the feasibility of TORS the retropharyngeal lymph node dissection with or without lateral oropharyngectomy. This technique has also been used in cases with papillary thyroid cancer and metastatic lymph nodes, in order to resect the RPLN metastases.

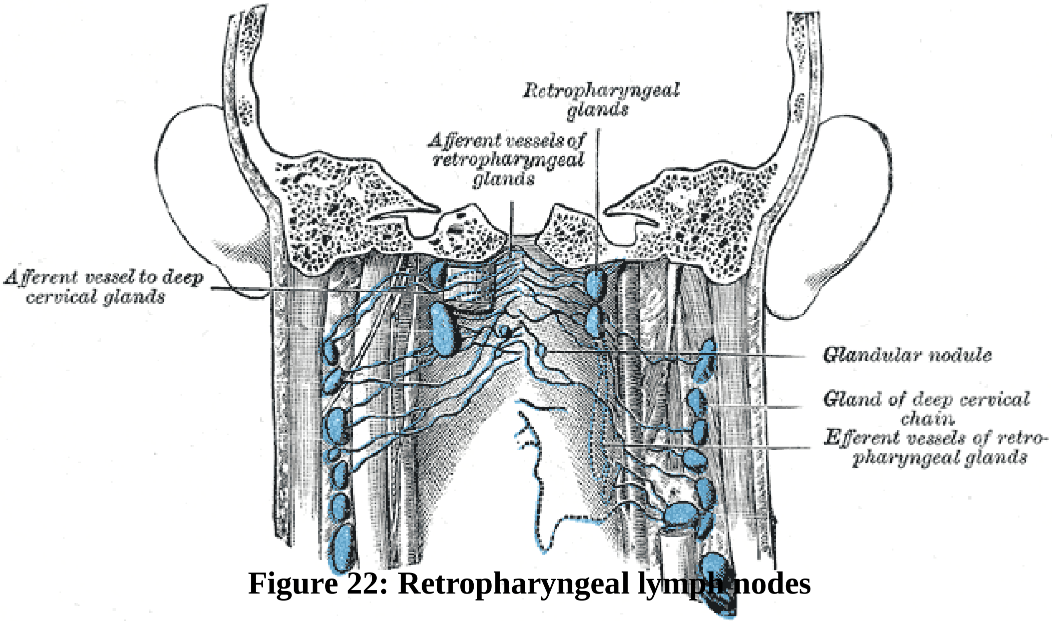


Figure 22: Retropharyngeal lymph nodes

5.7.3 Unknown primary tumors of head and neck

An experienced head and neck surgeon should evaluate a patient comprehensively, in order to to designate a primary tumor as a true unknown one. The evaluation is established with a thorough physical examination of the head and neck and then followed by a fiber-optic endoscopy of the regions of nasopharynx, oropharynx, hypopharynx and the larynx (86, 87). Approximately 52% to 55% of unknown primaries are diagnosed by an otolaryngologist, just after taking the patient's history and conducting their physical examination alone (87).

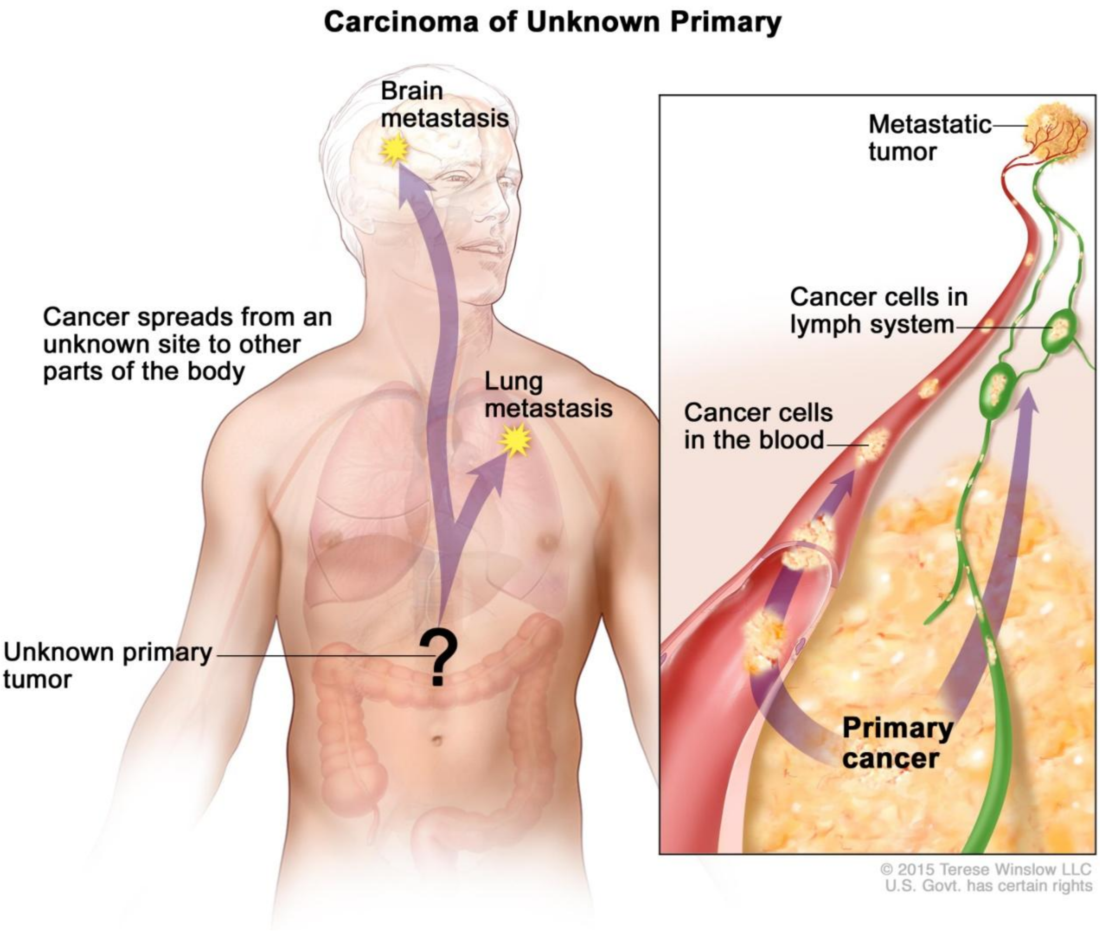


Figure 23: Carcinoma of Unknown Primary

After taking a biopsy from the suspected neck lesions, the tissue is then analyzed for HPV and p16 status. Typically the biopsy is obtained via fine-needle aspiration.

An important component of the workup for the unknown primary tumor is also the contrast enhanced CT and/or MRI with gadolinium. As a result a percentage of 17% to 31% of occult primary sites will be detected (87, 88). On the other hand though, when CT and/or MRI are unable to reveal an apparent primary site, the positron emission tomography (PET) either alone or fused with CT imaging (PET-CT), is used as an adjunctive modality. Recently a retrospective study showed that PET-CT has a detection rate of 36.8%, which is higher than the PET detection rate of 25%, as it averages in 16 different studies (89). Even though there is an improved specificity with PET-CT over PET (95% vs 75%), it is still prone to false positives because of the higher rate of metabolism in the lymphatic tissue of Waldeyer's ring, including of course the palatine and lingual tonsils (89).

However, the gold standard for the identification of the unknown primary tumors remains panendoscopy, which is a critical procedure for the diagnostic workup and is able to detect previously occult primary tumors in 16% to 26% of cases. (87) There are, though, mucosal abnormalities suggestive of malignancy that are often not observed during the procedure of panendoscopy and as a result lead, even in the absence of obvious abnormality, to the practice of “directed” biopsies in the regions of nasopharynx, tongue base, tonsils, and pyriform sinuses.

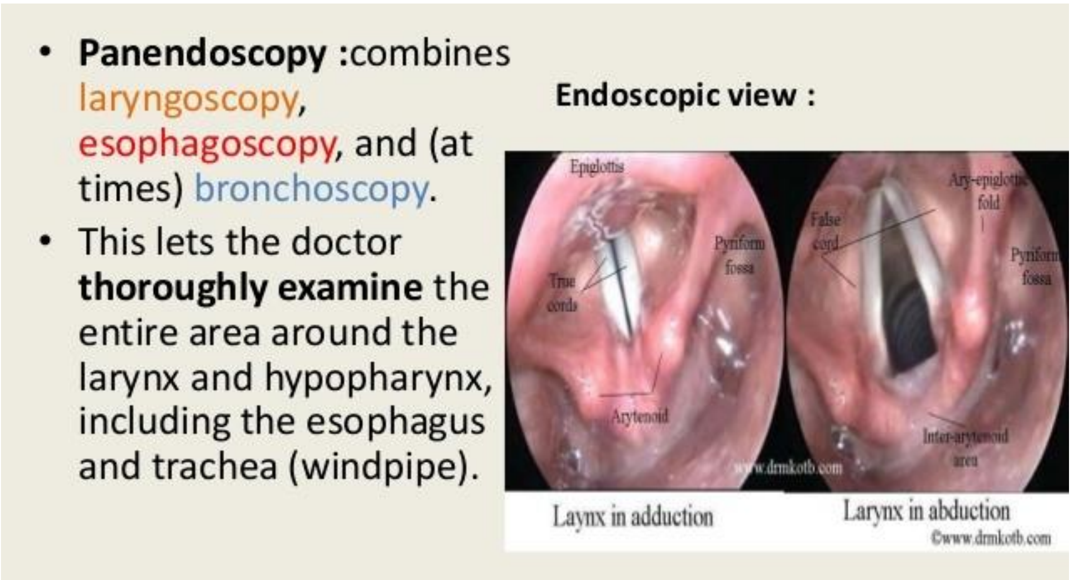


Figure 24: Panendoscopy: the gold standard for the identification of the unknown primary tumors

In one series, 9% of occult tumors were investigated on the basis of these directed or random biopsies (87, 90). The tongue base is the most common site for unknown primary tumors to be found (87). Usually a complete biopsy of the gross base of tongue is technically difficult with the use of traditional surgical instruments, in contrast to the tonsils. As a result, it is always crucial to palpate the tongue base and to visualize the subtle mucosal irregularities or areas of friability of the tongue base during the procedure of panendoscopy.

Almost 1% to 5% of squamous cell carcinomas of the head and neck appear as a cervical metastasis from an unknown primary tumor site (86). It still remains challenging to localize the unknown primary tumor, with fewer than 60% of primary tumors finally being revealed. There is no regulated approach to the management and evaluation of cancer of unknown primary (CUP), but it is well accepted that the recognition of the primary tumor site is of great importance. Transoral Robotic Surgery (TORS) has come up as a surgical tool that has upgraded the identification of the primary tumor site in patients who present with CUP. When the primary tumor sites are identified, then precise targeting of definitive or adjuvant radiation treatment follows, if it is indicated. TORS also allows precise surgical resection of occult tumors, which are often early T-classification tumors. Moreover, if the surgeon can localize and surgically resect the occult tumor, the use of adjuvant chemotherapy can be avoided in a subgroup of patients with CUP. If the primary site is confirmed in the frozen section analysis and it is subject to be cured through surgical resection, the proper transoral retractors are set in place and TORS resection can be applied.

i. Surgical management of unknown primary cancer

If the ENT surgeon fails to identify the primary site of tumor while performing direct laryngoscopy and esophagoscopy, TORS examination is then applied. In this case paralytic agents are given to the patient in order to assist in transoral exposure. The Crowe-Davis mouth gag (Storz, Heidelberg, Germany) is typically used for the visualization of the lingual and palatine tonsils. Sometimes the Feye–Kastenbauer (FK) retractor (Gyrus ACMI, Southborough, MA) can also be used, but this depends on the individual patient exposure. The procedure starts with the use of 0-degree 11-mm robotic camera and the ENT surgeon begins with the examination of the palate, palatine tonsil, posterior pharynx, glossotonsillar sulcus, and tongue base. The surgeon can also use the 30-degree camera in order to examine the tongue base. It is well established that examination with TORS technique provides a magnified, high definition view of the oropharynx. Therefore small primary tumors (which cannot be visualized otherwise with the traditional panendoscopy techniques) are able to be identified. However, although TORS has the significant advantage of excellent visualization on the one hand, on the other hand haptic feedback and the capability to palpate the suspicious regions is lacking. As the procedure is executed, if the surgeon identifies a suspicious area, then a biopsy is performed and the tissue is sent for frozen section analysis. If the surgeon though fails to identify a suspicious area after performing direct laryngoscopy and TORS examination, then it is indicated that he should carry out an ipsilateral radical palatine tonsillectomy and lingual tonsillectomy.

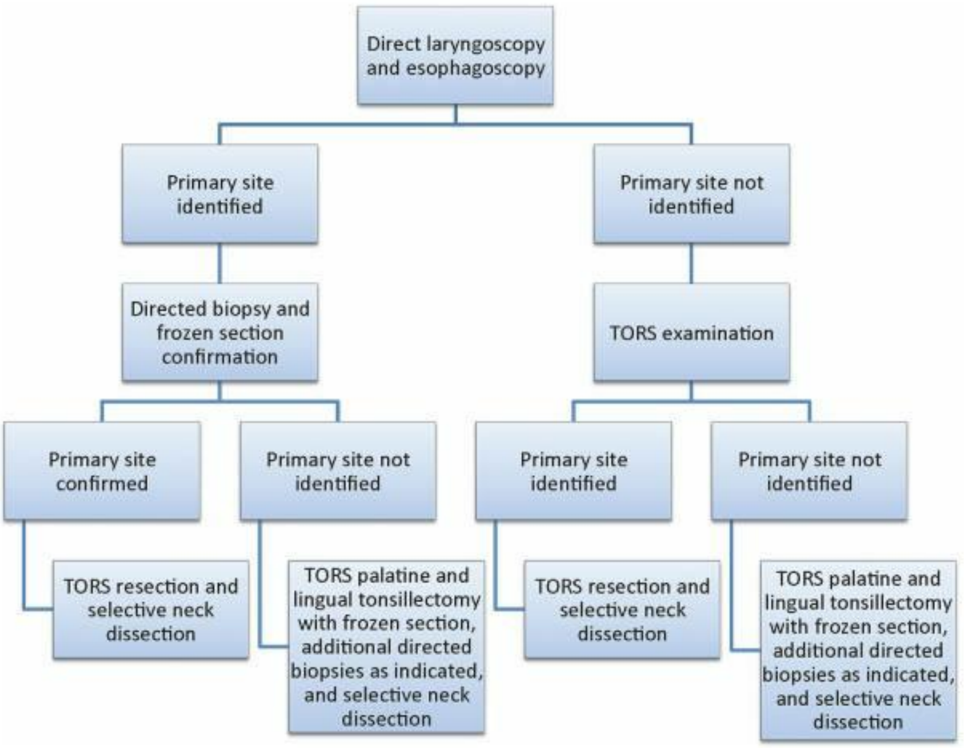


Figure 25: The algorithm of investigation that is followed

ii. Procedure

The necessary surgical tools for this procedure are: the 0-degree camera, the monopolar cautery and the Maryland dissector. The surgeon performs a radical palatine tonsillectomy after dissecting from superior to inferior, including the superior constrictor muscle as the deep margin of excision. After reaching the base of the palatine tonsil, the dissection is then taken medially, deep to the glossotonsillar sulcus, traversing the plane between the palatine tonsil and the lingual tonsil. As a result the palatine tonsil is left being connected to the lingual tonsillectomy specimen. The surgeon then performs the lingual tonsillectomy from lateral to medial, extending to midline, removing en bloc the entire ipsilateral palatine tonsil, glossotonsillar sulcus, and lingual tonsil. After that the specimen is transferred for frozen section analysis. If the pathologist identifies tumor positively in the specimen on frozen sections, additional resection may be indicated and defined by the location of the tumor. When a frozen section analysis is included within the surgical procedure followed, a potential therapeutic benefit of the TORS technique during the same surgical session can be achieved. Contralateral extracapsular palatine tonsillectomy can also be executed, leaving the superior constrictor muscle undamaged. In the primary site cannot be identified after the frozen section analysis has taken place, then permanent pathologic analysis is reviewed, as revision may reveal the primary site within the surgical specimen. After completing the TORS portion of the procedure the surgeon achieves hemostasis with the use of suction monopolar cautery. In several studies published so far, the surgeons do not routinely perform prophylactic ligation of the lingual artery or other branches of the external carotid artery (91).

The motive for this approach is that permanent section analysis may finally reveal a small primary tumor within the surgical specimen that was at the beginning missed on frozen section analysis. Secondly, when a surgeon performs selective neck dissection, valuable pathologic staging information can be provided, such as presence or absence of extracapsular spread. It is well known that this information cannot be precisely detected by imaging in HPV positive disease, as the CT scan does not constitute a reliable method for determining the presence of extracapsular spread (ECS) in p16-positive head and neck squamous cell cancer patients (92).

Durmus et al. (93) reported the use of TORS technique and published their results on 22 patients with unknown primary carcinomas treated with the approach described above. In this cohort, 80% were HPV positive; 91% were AJCC stage IV tumors, and the remaining patients (9%) were AJCC stage III. The authors identified the primary tumor site in 77% of patients (17 of 22), with the tumor being located in the palatine tonsil in 59% (13 of 22), and tongue base in 18% (4 of 22) of patients. Particularly of the 17 patients whose primary tumor site was investigated, 76.5% (13 of 17) were treated with complete TORS resection with negative surgical margins, procedure which provided not only important information for diagnosis but also significant therapeutic advantage from the TORS approach applied. Because of the fact that most patients were AJCC stage IV, their doctors delivered to them adjuvant treatment; 13 of 22 patients (59.1%) were capable of avoiding chemotherapy and therefore underwent adjuvant radiation treatment alone. On the other hand, 9 of 22 patients (40.9%) were treated with adjuvant chemoradiation.

Abuzeid et al. (94) announced a report where they described the use of TORS for a biopsy of the tongue base in patients with CUP. In this report, surgeons revealed an abnormal area at the tongue base by performing traditional panendoscopy; microdirect laryngoscopy was conducted with the use of a rigid endoscope and cup forceps was used for directed biopsies. However, frozen sections proved to be negative at this region. Afterwards the authors performed a unilateral TORS lingual tonsillectomy and the primary tumor site was then identified within this resection. However, surgeons only identified submucosal HPV positive squamous cell carcinoma in the deep tissue, even though no abnormality was defined in the overlying layers of mucosa. According to the authors, there was no doubt that the application of TORS allowed identification of the primary site and prevented wide-field radiation treatment, although some patients of this study finally received definitive radiation treatment to the primary site and bilateral neck regions.

Mehta et al. (95) announced a retrospective review of 10 patients with CUP who underwent TORS resection of the tongue base. In this cohort, patients underwent preoperative physical examination which included flexible laryngoscopy and

PET/CT. The investigation was accompanied with a traditional endoscopy, directed biopsies of the tongue base and bilateral tonsillectomy, without performing TORS. If the primary site was not diagnosed with this technique, the patient was then subjected to TORS resection of the bilateral lingual tonsils. TORS lingual tonsillectomy and directed biopsies managed to reveal the primary tumor site on permanent pathologic analysis in 9 of 10 patients whose primary tumor was not recognized by conventional endoscopy. One patient in this study had a positively identified, fully resected tongue base primary and underwent selective neck dissection with only one positive node. As a result he was treated with surgery alone. The residual 9 patients were treated with IMRT and concurrent chemotherapy. The authors argue that in patients whose CUP is not identified by examination under anesthesia (EUA) and palatine tonsillectomy, the majority of CUPs can be detected in the tongue base. Therefore, diagnostic TORS lingual tonsillectomy in these patients is recommended.

In another study by Motz et al (96), 84 patient with UPSCC (Unknown Primary Squamous Cell Carcinoma of the Head and Neck) were analyzed. The patients with HPV-positive UPSCC were significantly more likely to be younger (56.1 vs 67.7 years, P = .002) and male (91% vs 42.9%, P = .005), compared to the HPV-negative patients with UPSCC. In general the primary tumor site detection rate was 59.3% (n = 48). There was a minor rise in the detection rate from calendar periods 2005-2008 to 2012-2014 (50.0% vs 64.9%, P = .38). Since transoral robotic surgery was used in the diagnostic evaluation of UPSCC in 2011, a trivial increase in the investigation of primary tumors was noted (53.8% vs 64.3%, P = .34). According to this study, most cases are HPV-positive while the frequency of UPSCC has been raised considerably in recent calendar periods. As a result, authors conclude that patients with HPV-positive Unknown Primary Squamous Cell Carcinoma of the Head and Neck tend to be male and younger.

Patel et al studied another group of patients and managed to identify the primary tumor site in 72 % of them (who had no suspicious findings during their preoperative physical exam or imaging). In their study, authors applied TORS technique on the patients and conducted a retrospective multi-institutional case series afterwards (97). The authors compared their results to a study by Cianchetti et al. (98) where panendoscopy with directed biopsies and a unilateral or bilateral tonsillectomy were used. In the study of Cianchetti et al. there was a diagnostic rate of 29 % when there were no suspicious findings on pre-operative physical exam or radiographic evaluation. The authors reached the conclusion that TORS offers the advantage of identification of the primary tumor site as well as the definitive management of the tumor of unknown origin. This would inhibit the necessity for widefield irradiation to the upper aerodigestive tract. However the multi-institutional nature of this study does not allow a uniform paradigm to be applied. On the other hand though, this study provides a powerful sample size which definitely supports the advantages of TORS in the management of CUP, as well as its practicability.

When we compare TORS to traditional panendoscopy techniques, then a superiority of the TORS approach in the identification of the primary tumor site is revealed. When we apply traditional panendoscopy techniques without TORS, identification rates of the primary tumor site range from 25% to 57% (99-101). On the contrary, the studies discussed above show identification rates varying from 72% to 90%, even with a smaller size of sample (102, 103). As already discussed, the application of TORS in the diagnosis, as well as the management of CUP provides several advantages over traditional panendoscopy. Above all, the high definition robotic camera provides a magnified view of the oropharynx, permitting excellent visualization of the small primary lesions of the mucosa, which are otherwise difficult to be identified without being significantly magnified first. Secondly, TORS allows the diagnostic resection of the palatine and lingual tonsils even if the occult tumor cannot be visually identified and the specimen is then sent for frozen section analysis. This procedure presents a larger surface area with a greater depth of tissue to be sampled. Taking into consideration that a complete en bloc resection of the lingual tonsils is particularly difficult in the lingual tonsil, we can easily estimate the great value of the use of TORS.

Another application of TORS includes the technique of transoral laser microsurgery (TLM). TLM has also been successfully utilized in the identification and treatment of CUP (99, 104). Graboyes et al. studied a cohort of 65 patients with HPV positive CUP, who were treated with a TLM method (104). In their algorithm, patients (with primary site already identified with direct laryngoscopy and frozen section) undergo TLM resection to negative margins followed by neck dissection. When the surgeon fails to identify the primary site of tumor on initial endoscopy, ipsilateral TLM palatine and lingual tonsillectomy are executed and the specimens are sent for frozen section. If the specimens are proved positive for cancer, TLM resection is performed followed by neck dissection. If lingual and palatine tonsillectomy specimens are negative on frozen section, permanent sections are used to arrange the following therapeutic steps. In this study the authors report a primary site detection rate of 89%. In patients whose primary site was diagnosed, 5-year overall survival was 98% while the disease-specific survival was 97%. In patients whose primary site was not identified on the other hand, overall survival was 100%, although this group was small. It is noteworthy to state that, 26% of patients were treated with surgery alone. Of course there are several basic differences between TORS and TLM. However, the primary goal of the two surgical modalities in the treatment of CUP is the same: to identify and resect the occult primary site effectively, to reduce the radiation treatment applied, and to prevent chemotherapy in a subgroup of patients.

There is no doubt that there are several advantages when the primary site in patients presenting with CUP is identified. Identification of the primary site provides first of all the capability of focusing the radiation treatment field, and secondly the treatment doses can be decreased, reducing, of course, the radiation-related toxicities as well. When the primary site is not identified on the other hand, conventional radiation treatment to the whole upper aerodigestive tract for CUP tends to result in grade 3 dysphagia in approximately 50% of all patients (105). It is even more important to mention though, that identification of the primary site in patients with CUP has been shown to improve survival rates significantly (106-108).

It is well established that most HPV-related neck disease will arise from a primary site of the oropharynx (109). However, patients who present with CUP and suffer with HPV-positive neck disease should still be evaluated thoroughly in order to have their primary site of origin identified. If the primary site is not diagnosed, nonsurgical treatment cannot simply be limited to the oropharynx. This occurs because of the fact that HPV positivity has been demonstrated in the nasopharynx and hypopharynx, though to a significantly lower proportion than squamous cell carcinoma of the oropharynx (109,110). However, without the primary site being accurately confirmed, the regions of nasopharynx, retropharyngeal nodes, and hypopharynx cannot be excluded from the primary radiation treatment field based only upon HPV status.

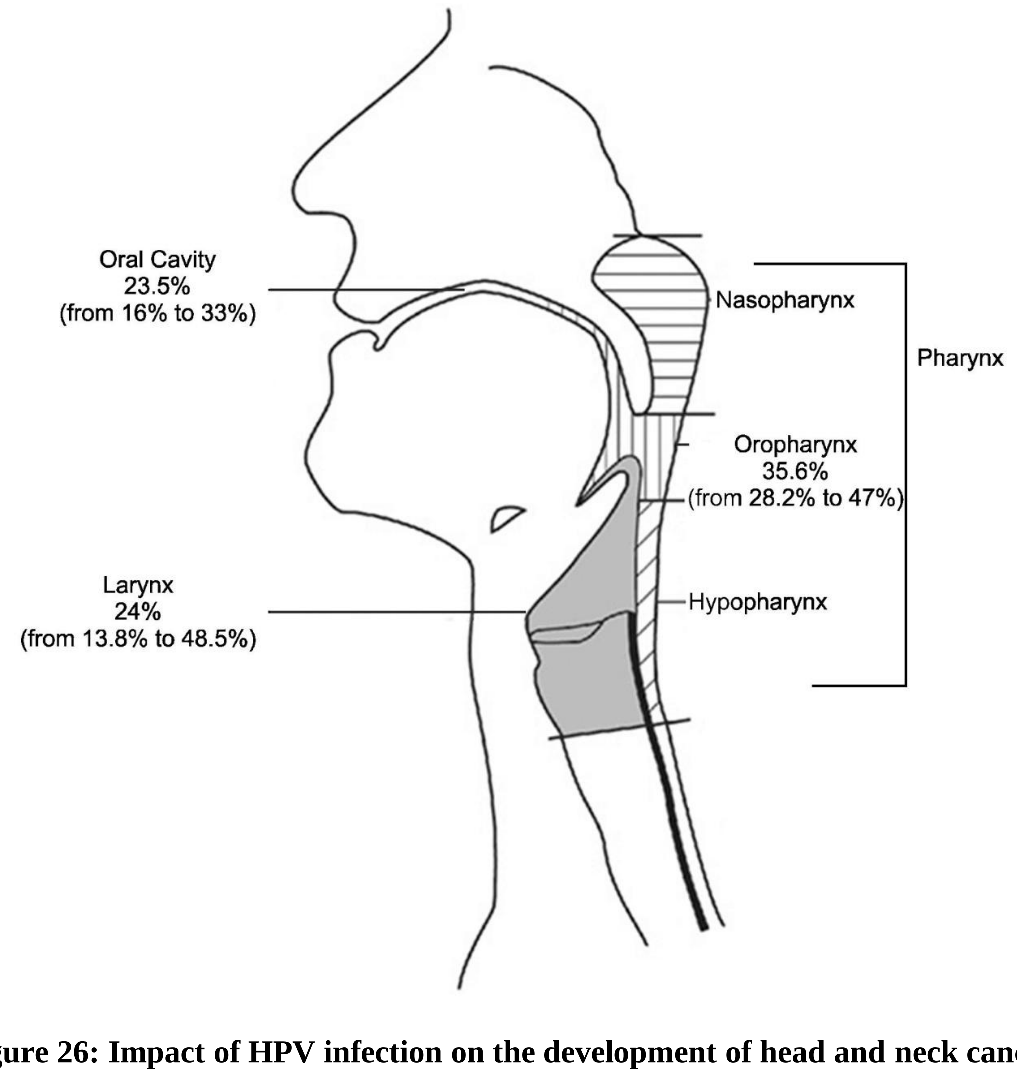


Figure 26: Impact of HPV infection on the development of head and neck cancer

In patients with N1 and some N2a neck disease and non-identified primary tumor in the oropharynx, ENT surgeons may think of applying surgical extirpation of the primary tumor and, as follows, neck dissection without adjuvant chemotherapy or radiation. When adverse pathologic features are present though, patients should definitely require adjuvant treatment. However, as opposed to covering all potential primary sites, the radiation doses can be reduced and can then be focused on the primary tumor site. Those with more advanced neck disease (N2/N3) and no evidence of extracapsular spread may also be treated with unilateral comprehensive neck dissection, accompanied with targeted mucosal irradiation of the oropharynx, as well as with bilateral neck irradiation. In these patients, the potential to avoid chemotherapy as part of their treatment along with focused radiation can be offered, as soon as the primary tumor is identified and a neck dissection is performed. At present, up-front concurrent chemoradiation is a progressively used alternative, even in these patients (111).

When the unknown primary tumor site is pinpointed, the significant morbidity associated with concurrent chemoradiation can potentially be spared. In up to 10% of patients with CUP metastatic spread from the contralateral palatine tonsil is present (112). Consequently, this is the reason why a contralateral tonsillectomy is suggested in these cases.

Although TORS constitutes a valuable diagnostic tool in the management of CUP, several authors would agree that its greatest advantage is in the capability of treating these early T classification primary tumors with primary surgery. If an ENT surgeon can achieve complete surgical resection at the primary site and is able to perform selective neck dissection as well, then adjuvant treatment may be deintensified to radiation treatment alone and even surgery alone in select cases. Chemotherapy was prevented in almost 59% of patients that would have otherwise received concurrent chemoradiation, assuming that nonsurgical treatment options were used (93).

All these data are fascinating enough to support the use of TORS in the management of CUP, especially in cases where either the primary site of the tumor localization, or the potential for surgical resection with negative margins may prevent the use of chemotherapy in a large number of CUP patients. Another crucial gain of a primary surgical approach is the additional pathologic information that is provided by selective neck dissection. Unfortunately CT imaging has been proved to be incorrect in the detection of extracapsular spread in HPV positive disease (113). Therefore, adjuvant chemotherapy is indicated. Maxwell et al. (113) reported in their study that the positive predictive value of CT scans ranged from 72% to 82% (when used for the detection of extracapsular spread in HPV positive disease), while the negative predictive value was only 53%. Hence, the authors believe that direct surgery provides crucial information regarding the pathologic staging of the tumor, which could direct an appropriate adjuvant treatment.

As TORS applies to CUP, its greatest disadvantage is undoubtedly the lack of haptic feedback of the robotic system used. It is true that the high definition optics of the robotic system and the magnification achieved can significantly improve visualization, but the inability of the surgeon to palpate tissue constitutes a severe drawback, particularly in tumor identification. As a result, it is critical that the surgeon is able to perform a traditional direct laryngoscopy and esophagoscopy, along with a careful palpation of the oropharynx (in the clinic and in the operating room) additionally to TORS examination.

TORS has first of all the ability to scale down the effects of adjuvant therapy by lessening the fields and doses of radiation treatment. Secondly, the use of TORS can potentially prevent the need of chemotherapy in a subset of patients and may allow the identification of the primary tumor site. Thus, a wide-field radiation treatment is prevented.

6. CONCLUSION

Apart from the well known application of TORS in T1 and T2 orophraryngeal tumors, other emerging applications have come forth into notice by several pioneers of transoral robotic surgery in different centers around the world. At the moment, TORS is changing significantly the number of unknown primary tumors of head and neck that is diagnosed, whereas it permits less invasive surgical techniques in cancer of advanced stage. Surprisingly, TORS has been proved to be superior to the procedure of panendoscopy, particularly when treating tumors of head and neck region that are accessed with difficulty or when the potential for surgical resection with negative margins may prevent the use of chemotherapy.

The new generation of robots is going to extend the usage of TORS in the years to come. Definitely, though, more series of patients and studies with long-term results are needed in order to prove the advantages of transoral robotic surgery, compared to conventional surgical techniques or other adjuvant therapies like RT and chemotherapy.

TABLE 1: ***Population characteristics and data of the included studies***

Author	Patient number	T1-T2	T3/T4 %	hpv +	hpv-	Tongue base	Tonsil	Soft palate	Oropharyngeal wall	Lingual tonsil	Occult	Supraglottic	Diagnosis for Cup %	Unknown primary	Pps	Retromollar Trigone	Stage %	Close margins: Yes	Close margins: No	Retro-pharyngeal M	Peg temp.	Trache temp.	lc	Overall survival	1y	2y	survival for hpv +	survival for hpv -
Moore et al.	66	52	18	44													88						97			92		
White	89	69	20														73						97					
Weinstein et al.	47		22														76				2	11	98					
Weinstein et al.	27	21	6				27																					
Desai et.	8	8				2	2	2				2																
Boudreaux	19	Recurrence T1-T2																										
Moore et al.	45	33	12			26	19														34	14				92		
Hurtuk	66	10	44	37	9	6	47			5						1												
Multicenter study	364	303	61	159	70	115	165	123										86	170									
Moore et al.	72	59	7	60	12	17	55													8								
Alabama USA	65	57	8	51	14	21	38	0	6									15										
Weinstein et al.	30	25	5			9	14	3	1	3								1	29									
Pittcburg	34	33	1																									
Dziegielewski	81	73	8	51	30																							
Hammudi et al.	26	22	4				19																					
Dean et al.	15	15																										
Gender et al.	31	31																										
Moore et al.	148	148																										
Sinclair et al.	42	42																										
Sydney H&N cancer Inst.	92	92							9															83 % 5y				
Hospital de la crois Rousse	53	53																						73 % 5y	100			
University de Paris	191	191																			58,6	3,7						
Kukur et PPS	73	66	7			13	60																					
Lörincz BB et Germany	35	35																										
Marcante G italy	13	13				13																			100			
Blanco et al.	35	30		23	7									3													91	71
Cohen et al.	50			37	13																						91	71
Olsen et al.	18			18																							100	
Kaczmar , O'malley	114	104	10			43	6											26	88									
Mehta V	10													10														
Channir	13									7			54	13														
Teknos et al.	23	15	1			4	12			4	6			23														
Patel SA	47					20							72	47														
Durmus et al.	3															3												
Chan et al.	44														29 pleomorhic													
Park et al.	9														9													
Arsdam	3														3													

ABSTRACT

Background: So far standard treatment for patients with oropharyngeal cancer has been surgery, in some cases including Radiation Therapy and/ or neck dissection. According to epidemiological studies however, there has been an increase in the incidence of oropharyngeal cancer. As a result the role of the Da Vinci robot has also increased dramatically because of additional developments and refinements, and it has been used for a wide range of procedures in the head and neck, particularly transorally.

Aim: The aim of our study is a review of literature on all emerging applications of transoral robotic surgery (TORS) in oropharyngeal malignancies.

Methods: Articles were identified through the following keyword searches: "transoral robotic surgery", "oropharyngeal cancer", "oropharynx and TORS", "unknown primary', "TORS and retropharyngeal space'' and "TORS and tongue base". 2011 reviews for SCC oropharyngeal cancer and all available publications for all the other emerging oropharyngeal applications were analyzed. Abstracts, case reports, expert opinions, as well as non-English publications were excluded. The complete search yielded 27 studies, published until January 2016.

Results: The total number of patients in all trials was 1729. From the articles analyzed there were 36 series of patients who underwent TORS for different sub sites of oropharyngeal cancer.

Conclusions: TORS changes significantly the number of unknown primary tumors of head and neck that is diagnosed, whereas it permits less invasive surgical techniques in cancer of advanced stage. Surprisingly, TORS has been proved to be superior to the procedure of panendoscopy, particularly when treating tumors of head and neck region that are accessed with difficulty (e.g. tongue base, retropharyngeal space etc), or when the potential for surgical resection with negative margins may prevent the use of chemotherapy and/ or may lessen the fields and doses of radiation treatment.

Key words: transoral robotic surgery, oropharyngeal cancer, unknown primary, retropharyngeal space, tongue base

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Μέχρι στιγμής η καθιερωμένη αντιμετώπιση των ασθενών με καρκίνο του στοματοφάρυγγα είναι χειρουργική, συχνά σε συνδυασμό με ακτινοθεραπεία ή/και λεμφαδενικό καθαρισμό. Σύμφωνα με τις επιδημιολογικές μελέτες, όμως, παρατηρείται πλέον μια αυξημένη επίπτωση του καρκίνου του στοματοφάρυγγα. Έτσι λοιπόν λόγω πρόσθετων εξελίξεων, ο ρόλος του ρομποτικού συστήματος Da Vinci έχει πολλαπλασιαστεί δραματικά, ενώ εφαρμόζεται σε μια πλειάδα επεμβάσεων στην κεφαλή και τον τράχηλο, ιδίως διαστοματικά.

Σκοπός: Σκοπός της παρούσας μελέτης είναι η διεξαγωγή ανασκόπησης στη βιβλιογραφία, όσον αφορά τις αναδυόμενες ενδείξεις εφαρμογής της διαστοματικής ρομποτικής χειρουργικής (TORS) στις κακοήθειες του στοματοφάρυγγα. .

Μέθοδοι: Τα άρθρα εντοπίστηκαν μέσω αναζήτησης των ακόλουθων λέξεων-κλειδιών: «διαστοματική ρομποτική χειρουργική», «καρκίνος στοματοφάρυγγα», «οροφάρυγγας και TORS», «άγνωστο πρωτοπαθές», «TORS και οπισθοφαρυγγικό διάστημα» και «TORS και ρίζα γλώσσας». Αναλύθηκαν 2011 μελέτες για τον καρκίνο του στοματοφάρυγγα και όλες οι δημοσιεύσεις για τις αναφαινόμενες ενδείξεις εφαρμογής του TORS. Εξαιρέθηκαν περιλήψεις, μεμονωμένα περιστατικά, οι απόψεις των εμπειρογνωμόνων και οι μη αγγλόφωνες δημοσιεύσεις. Τελικά μελετήθηκαν 27 άρθρα, δημοσιευμένα έως τον Ιανουάριο 2016.

Αποτελέσματα: Ο συνολικός αριθμός των ασθενών σε όλες τις μελέτες ήταν 1729. Στα άρθρα που αναλύθηκαν, υπήρχαν 36 σειρές ασθενών που υποβλήθηκαν σε TORS για καρκίνο στοματοφάρυγγα διαφορετικής εντόπισης.

Συμπεράσματα: Η διαστοματική ρομποτική χειρουργική αλλάζει σημαντικά τον αριθμό των καρκίνων αγνώστου πρωτοπαθούς που διαγιγνώσκονται, ενώ επιτρέπει τη λιγότερο επεμβατική χειρουργική τεχνική σε καρκίνο προχωρημένου σταδίου. Επιπλέον, φαίνεται να υπερέχει διαγνωστικά της πανενδοσκόπησης, ιδίως σε περιπτώσεις όγκων κεφαλής και τραχήλου που προσεγγίζονται δύσκολα (π.χ. βάση γλώσσας, οπισθοφαρυγγικό διάστημα κτλ), ή όταν η δυνατότητα εξασφάλισης αρνητικών ορίων εκτομής, ίσως συνεπάγεται αποφυγή χημειοθεραπείας ή/και ελάττωση της δόσης και των πεδίων ακτινοβόλησης.

Λέξεις- κλειδιά: διαστοματική ρομποτική χειρουργική, καρκίνος στοματοφάρυγγα, άγνωστο πρωτοπαθές, οπισθοφαρυγγικό διάστημα, ρίζα γλώσσας

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