Review

Transoral Robotic Surgery and the Unknown Primary

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Abstract

Carcinoma of unknown primary (CUP) comprises approximately 1%–5% of all head and neck malignancies. Primary site detection rates for metastatic cervical squamous cell carcinoma (SCC) remain variable, with current diagnostic imaging unable to identify all tumours. Prevailing evidence suggests that most head and neck CUP are located in the oropharynx. Diagnostic surgical efforts have been directed at sampling the entire oropharynx. Present techniques that make this possible include transoral robotic surgery (TORS). TORS Lingual tonsillectomy or tongue base mucosectomy performed in the setting of head and neck CUP increases the detection rate of occult tumour. The indication, surgical technique, evidence base, and controversies of performing TORS in the context of the unknown primary are presented.

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Introduction: The Unknown Primary

Carcinoma of unknown primary (CUP) comprises approximately 1%–5% of all head and neck malignancies [1–3]. These patients present with cervical lymphadenopathy that is biopsy proven for carcinoma, but no obvious primary tumour is identified following thorough clinical examination and appropriate investigations. Of these unknown primaries, over 90% represent squamous cell carcinomas (SCC), with adenocarcinoma, melanoma, and rarer histological subtypes making up the rest [4]. The majority of these cancers are small (<1 cm)

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tumours arising in Waldeyer's ring, i.e. lymphoid tissue of the nasopharynx, tonsil, and base of tongue [5], particularly in the oropharyngeal region, and especially amongst patients who are high-risk human papilloma virus (HPV) positive [6–8]. Even with advanced diagnostic workup the primary tumour location remains unknown in over 40% of cases [9–11].

The natural history of CUP is unclear, making diagnosis and management planning particularly difficult in these cases. Identification of the primary tumour is essential as its discovery allows the patient to receive site-specific treatment, avoiding wide-field radiation side effects [12], or the additional morbidity associated with surgical intervention. Primary tumour site detection is also associated with better oncological outcomes [13].

Diagnostic Workup

The typical protocol for diagnosing head and neck CUP includes a comprehensive clinical examination, followed by computed tomography (CT) and/or magnetic resonance imaging (MRI), then panendoscopy or examination under anaesthesia +/- blind biopsies of suspected mucosal areas in the nasopharynx, oropharynx, and hypopharynx, plus ipsilateral or bilateral palatine tonsillectomy [14]. Ipsilateral palatine tonsillectomy alone detects 18%–44% of occult tumours [15–17], whereas some authors have reported contralateral palatine tonsil tumour detection in 10%–23% of patients [17–19]. Whilst most cancer centres have an established diagnostic protocol for head and neck CUP as described above, primary site detection rates for metastatic cervical SCC remain variable, with current techniques not able to identify all tumours. CT or MRI detection rates of the primary tumour ranges from 9%–23% [9, 20]. Clinical and radiological examinations can only guide endoscopic biopsy so far, providing successful detection of a primary in only 20%–29% of cases [14, 21]. The detection rate via endoscopic-guided biopsy is much higher when there is clinical or radiological evidence of a lesion, with rates rising as high as 60% [3, 14].

The use of [¹⁸F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) combined with CT imaging (FDG-PET-CT) in the diagnosis of CUP, is playing an ever-greater role in the detection of a primary tumour. This nuclear medicine scan involves injecting a glucose analogue followed by whole body imaging to identify any distant metastases as well as the extent of spread through the head and neck region. [¹⁸F]-FDG is the most commonly used radiopharmaceutical due to its preferential uptake by cells with rapid turnover, such as malignant cells [22]. The use of PET-CT in the evaluation of head and neck CUP is now accepted as a key component of the diagnostic protocol, performed prior to panendoscopy and permitting targeted biopsy of suspicious lesions. PET-CT provides additional primary tumour detection rates over conventional imaging techniques of between 37% [22] and 44% [23] with a sensitivity of up to 97% and low specificity of 68% [23]. However, FDG-PET-CT is limited by its inability to detect small (sub-centimetre) tumours [24, 25] and normal physiological tracer uptake by tissues such as salivary glands, lymphoid tissue, and muscle can result in a high false-positive rate. False-negative results can occur in situations where pathological [¹⁸F]-FDG uptake is considered physiological [24].

Diagnostic Transoral Surgery

Current evidence suggests that most head and neck CUP are located in the oropharynx [9, 14, 26], hence additional diagnostic efforts have been directed at sampling the entire oropharynx, by removing the palatine and lingual tonsils for histological assessment. Current techniques that make this possible are transoral laser microsurgery (TOLM) and transoral

robotic surgery (TORS). TOLM and TORS provide superior visualisation and instrumentation over conventional techniques, and permit resection of the entire tongue base mucosa and lingual tonsils that would be technically challenging using traditional surgical approaches. Lingual tonsillectomy performed in the setting of head and neck CUP increases the detection rate of occult tumour when conventional clinical assessment, imaging (CT/MRI/PET-CT), panendoscopy + blind (random) biopsies, and palatine tonsillectomy have failed to identify the primary site [27].

The systematic review by Fu et al. [27] highlights the incremental benefit of lingual tonsillectomy by TOLM or TORS in the detection of occult primary head and neck SCC when comprehensive diagnostic workup of clinical examination, cross-sectional imaging, PET-CT and panendoscopy + tonsillectomy + blind biopsies does not yield the primary tumour. From the 8 studies (2 TOLM and 6 TORS) that met inclusion criteria for subsequent analysis, lingual tonsillectomy provided incremental primary tumour detection in 72% of patients where no abnormal findings had been detected with comprehensive diagnostic assessment including PET-CT, examination under anaesthesia plus biopsies, and palatine tonsillectomy. In addition, contralateral tongue base carcinoma was identified in 6% [27] to 12% [28] of patients, supporting the need for bilateral tongue base lingual tonsillectomy as part of the comprehensive workup for CUP. As per bilateral palatine tonsillectomy, the additional morbidity from a contralateral lingual tonsillectomy needs to be considered. Overall morbidity from TOLM and TORS lingual tonsillectomy was low, with a 5% rate of post-operative haemorrhage as the main complication [27]. The systematic review by Fu et al. [27] is however limited by the small sample size of included studies, inter-institutional and inter-surgeon variation in the technique for performing TOLM or TORS lingual tonsillectomy, and publication bias, with institutions that have recorded favourable results more likely to publish their data.

The additional diagnostic yield of TOLM and TORS for head and neck CUP has prompted some authors to recommend upfront lingual tonsillectomy at the time of panendoscopy + biopsy, instead of following negative targeted biopsies of the oropharynx [8, 29, 30]. This has been shown to be a more cost-effective approach from reductions in delays to diagnosis, and the additional expense of a second operation. Disadvantages of this approach include unnecessarily longer operating times for the proportion of patients positive for carcinoma elsewhere in the upper aerodigestive tract, and the additional morbidity associated with a lingual tonsillectomy [27].

TOLM versus TORS Lingual Tonsillectomy

TOLM and TORS are both effective surgical tools for performing a lingual tonsillectomy in the context of CUP. TOLM alone has enhanced occult tumour detection rates following lingual tonsillectomy of 61%–68% [8, 30] versus 51%–100% for TORS lingual tonsillectomy [28, 31–36]. Compared to TOLM lingual tonsillectomy, TORS has the added advantage of superior three-dimensional (3D) high-definition visualisation, wider range of instrument motion with seven degrees of freedom plus the ability to manoeuvre around corners with the help of angled scopes, significant reduction in hand tremors, decreased fatigue, and improved hand-eye coordination [35, 37].

TORS Lingual Tonsillectomy

TORS lingual tonsillectomy or base of tongue “mucosectomy” is a novel surgical technique, which has recently, within the past 5 years, found favour in the diagnostic workup of head and neck CUP [27]. The daVinci Surgical Robotic System (Intuitive Surgical Inc., Sunnyvale, CA, USA) is currently the most commonly used commercially available surgical robot; however, new entrants to the market such as the Medrobotics Flex® Robotic System (Medrobotics Corp., Raynham, MA, USA) are also available. One of the first authors to describe

Fig. 1. Anatomy of the oropharynx. **a** View of the tongue in normal position. **b** View of tongue base in the “operative position” with resection margins of the lingual tonsils or base of tongue mucosectomy outlined using a solid black line.

the novel procedure of TORS lingual tonsillectomy were Mehta et al. [35], and the surgical technique will be described in more detail later.

TORS Lingual Tonsillectomy Procedure Description

Patient Selection

Patients with T0N+M0 head and neck SCC CUP are selected, following comprehensive clinical assessment by a head and neck surgeon, cross-sectional imaging (CT or MRI), and PET-CT. They may have had a previous panendoscopy + blind biopsies +/- palatine tonsillectomy. Informed consent would have been obtained and the patient deemed fit for general anaesthesia, with no history of bleeding disorder nor recent anti-coagulation therapy.

The operating theatre set-up has been described in previous TORS publications [35, 37].

The patient is placed in the supine position, and following induction of anaesthesia, the operating table is turned 180° from the anaesthetic machine. The oropharynx is inspected and palpated to exclude any obvious lesions amenable to biopsy, and exposure to the base of tongue is obtained with a flat blade Boyle-Davis gag or Feyh-Kastenbauer retractor.

Robot Docking

The da Vinci robot is docked at the patient’s right side, and a 30° high-definition upward facing 3D endoscope is introduced into the oropharynx. The robotic instruments used in the lead author’s institution are the 8-mm fenestrated bipolar graspers on the left side, and the 8-mm monopolar cautery spatula on the right side. Depending on the da Vinci platform, a 5-mm Maryland grasper can also be used instead of the fenestrated bipolar grasper, and likewise a 5-mm monopolar cautery can be substituted for the 8-mm instrument.

Surgical Procedure

The anatomical boundaries of the resection are outlined in Figure 1. The procedure is performed according to Mehta et al. [35] with minor modifications to include a slightly deeper

Fig. 2. Intra-operative photos of TORS (right) base of tongue mucosectomy. **a** Initial vertical incision in midline of tongue base mucosa. **b** Superior (horizontal) incision posterior to circumvallate papillae. **c** Deeper sharp (monopolar) dissection onto muscle layer. **d** Resection of right base of tongue mucosectomy specimen, with accompanying defect up to vallecula (epiglottis highlighted with *).

ipsilateral (muscle) resection margin, following recent published data from Geltzeiler et al. [38]. Monopolar settings are usually at 20–25 W.

The initial (vertical) incision is made in the midline of the tongue base with monopolar cautery from the level of the circumvallate papillae down to the level of the vallecula (Fig. 2a). This incision is carried through to the muscular layer, but not through it on the contralateral side. The superior (horizontal) incision is from the midline to the level of the glossotonsillar sulcus (Fig. 2b). The plane of dissection just below the muscle layer on the ipsilateral side is maintained all the way down to the vallecula in a medial to lateral direction (Fig. 2c, d).

An important technical point to consider is that, whilst traction is vital to delineate the plane of dissection, it is important to initially develop a deep enough incision down to the muscle layer, before grabbing the superior aspect of the specimen with the fenestrated grasper, in order to minimise mucosal trauma and bleeding. The surgical assistant can help by providing counter pressure on the base of tongue, which delivers the tongue base into the surgical field. The depth of resection, as mentioned earlier, includes a small “sliver” of the muscular layer on the ipsilateral side only. Note, because the lingual tonsils are not encapsulated there is no “clear” plane of dissection, unlike that usually obtained during a palatine tonsillectomy. Therefore the plane of dissection during TORS lingual tonsillectomy or base of

tongue mucosectomy is not as readily apparent and must be developed through sharp dissection. Once the appropriate hemi-base of the tongue mucosectomy specimen has been excised, it is also important to remember its orientation prior to removal from the surgical field, and that this orientation should be noted for communication to the pathologist. Haemostasis is obtained with bipolar cautery to the surgical bed. Additional measures to prevent post-operative bleeding include application of haemostatic agents such as thrombin and gelatin foam to the base of tongue.

If TORS lingual tonsillectomy is performed together with TORS palatine tonsillectomy, the authors prefer to perform the lingual tonsillectomy component of the operation first. The inevitable tongue swelling that occurs due to prolonged compression from oral gag placement for access may make TORS lingual tonsillectomy more challenging.

Post-Operative Care

Patients are nursed on the ENT ward and encouraged to resume normal oral intake as soon as they have recovered from general anaesthesia. The tongue base is very sensitive and patients do require strong analgesia with or without a short course of oral steroids to facilitate pain control. Nasogastric tube placement for nutrition is very rarely required, and most patients are discharged home on the day after surgery.

Controversies: Why Perform TORS Lingual Tonsillectomy for the Unknown Primary?

If the Primary Tumour Is Identified

With TORS base of tongue mucosectomy providing additional primary tumour detection rates of 50%–90% after all other diagnostic modalities have failed [27, 28, 34, 38], increased survival rates may be achieved [2], and radiation fields can be limited to the affected oropharynx only, thus minimising the morbidity of radiotherapy treatment to patients. In addition, if the tumour is well lateralised in the tongue base, some tumour boards or head and neck cancer multidisciplinary teams may advocate omitting contralateral neck irradiation. Another benefit from positive identification of a small tongue base cancer is that the patient is now eligible for entry into treatment de-escalation trials, such as PATHOS [39].

If the Primary Tumour Is Not Identified after TORS Lingual Tonsillectomy

Because the entire oropharynx has been appropriately mapped, i.e. both palatine tonsils and base of tongue mucosectomy (or lingual tonsils) negative for carcinoma, further treatment can be tailored to the neck disease. For instance, N1 or N2a disease with no extracapsular spread and confirmed to be p16 or high-risk HPV positive may be treated with observation alone following neck dissection. If there are adverse pathological features in the neck dissection, such as extracapsular spread or a large number of positive lymph nodes, the patient may receive (chemo)radiotherapy to the neck only, sparing the oropharynx unnecessary treatment.

However, the argument against performing TORS base of tongue mucosectomy for an unknown primary would be the additional costs required for the robot and its consumables, which if not already available at a hospital can run into millions of dollars. There is also the technical expertise required to perform the procedure for which the learning curve is not insignificant. Finally, the additional patient morbidity from pain, short-term swallowing dysfunction, additional bleeding risk, and small risk of pharyngeal stenosis need to be considered. Thankfully, published studies from several international centres have shown that the morbidity from robotic base of tongue mucosectomy is low [27, 28, 34, 38].

Conclusion

Head and neck SCC of unknown primary remains a diagnostic and management challenge. The increasing incidence of p16 or high-risk HPV-positive oropharyngeal SCC has made this phenomenon more common for the head and neck cancer multidisciplinary team. TORS lingual tonsillectomy or tongue base mucosectomy is a novel surgical procedure that has significantly improved the detection rate for small base of tongue SCC, where conventional diagnostic techniques have failed. The procedure is relatively straightforward for appropriately trained robotic head and neck surgeons with low patient morbidity.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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