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Trans-oral robotic assisted tongue base mucosectomy for investigation of cancer of unknown primary in the head and neck region. The UK experience

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Running Title: Trans-oral robotic mucosectomy for the unknown head and neck primary.
Key words: TORS, Robotic, unknown primary, Head and Neck
Abstract

Introduction

The diagnosis of cancer of unknown primary (CUP) in head and neck occurs when the treating clinicians have utilised all available diagnostic tests and failed to identify the origin of the disease. There is no agreed consensus on which diagnostic investigations to use, or the order to use them in, although broad recommendations exist. Small tumours arising in the tongue base can be below the limits of resolution of conventional diagnostic techniques. Given the difficulty in targeting the tongue base, current practice involves blind random biopsies, which leads to a variable detection rate.

Robotically assisted surgical removal of the tongue base, termed tongue base mucosectomy (TBM), has been shown to improve diagnostic yield. This study reports the diagnostic hit rate for tongue base primaries using this technique from three centres in the UK.

Methods

Thirty-two patients from three UK head and neck cancer centres were classified as CUP after clinical examination, cross-sectional imaging, PET-CT as well as tonsillectomy and guided biopsies failed to identify a primary tumour.

Results

The primary tumour site was identified in the tongue base in 53% (n=17) of patients. In 15 patients the tumour was in the ipsilateral tongue base (88%) while in two cases (12%) the tumour was located in contra lateral tongue base.

Conclusion

Trans-oral robotic assisted TBM raises the possibility of identifying over 50% of tumours that would otherwise be classified as CUP. Identifying these in the contralateral tongue base has implications for treatment planning and outcome.
Introduction

Detection and assessment of the primary site remains a central strategy in the diagnostic evaluation of head and neck squamous cell cancer (HNSCC). Squamous cell carcinoma in a cervical lymph node with no identifiable primary site occurs in 2-4% of new head and neck cancer diagnoses. Techniques to find the primary site have evolved over time as technologies and understanding of the disease process have improved.

The definition of cancer of the unknown primary (CUP) is not fixed and reflects in part the number and type of investigations performed to identify the tumour. Once a tumour has been identified it is no longer a CUP. There is no internationally agreed consensus for the diagnostic investigations that need to be used or the order to use them in, however recent NICE guidelines in the UK have recommended a diagnostic algorithm. All patients should undergo a comprehensive physical examination including flexible nasendoscopy, this may be supplemented by trans-nasal oesophagoscopy and newer endoscopic modalities that use lights at different wavelengths to enhance the submucosal vasculature, such as narrow band imaging. Thereafter a variety of radiologic imaging modalities are employed including CT, MR and PET-CT, each with increasing sensitivity and specificity for identifying CUP. Cytology from a fine needle aspiration biopsy and/or tissue from a core biopsy is used to establish the diagnosis of metastatic squamous cell carcinoma. Clinical guideline documents recommend the use of high risk human papillomavirus (HR-HPV) testing and Epstein Barr virus (EBV) testing. These laboratory tests can be used to establish the likely site of the primary tumour: HPV, oropharynx: EBV, nasopharynx. Accumulating clinical experience suggests that the majority of CUP are HPV-related squamous cell carcinomas and are typically located in the palatine tonsil or the lingual tonsils of the tongue base.

Examination under anaesthesia ‘panendoscopy’ has been a mainstay of the investigative work-up for this patient group, preferably done after all radiologic imaging and biopsies of the nasopharynx, hypopharynx and oropharynx are frequently undertaken. These biopsies can be directed if there is
an identifiable area of abnormal mucosa, but in other cases are directed at known ‘high risk’ areas. Performing a palatine tonsillectomy rather than a deep biopsy has also improved the diagnostic yield as a number of small tumours are within the tonsil crypts\textsuperscript{(9)}. While some studies have reported 10-17\% of tumours arising in the contra lateral tonsil there remains no consensus on performing a unilateral or bilateral tonsillectomy. \textsuperscript{(10, 11)}

These investigations will identify a primary tumour in around a third of patients. For the other patients, classified as CUP, there is the spectre of undetected disease, with potential impact on quality of life and survival \textsuperscript{(12)}. Without identifying a primary tumour it is likely the patient will receive wide field radiotherapy with or without chemotherapy, with the extent of the irradiated mucosa varying from ipsilateral oropharyngeal mucosa, to all oropharyngeal mucosa sparing the nasopharynx, to complete upper aerodigestive tract mucosal irradiation\textsuperscript{(13)}. The nodal groups in the neck, on one or sometimes both sides, are always in the radiation fields. The extent of radiotherapy treatment has a direct impact on functional and long-term outcomes. \textsuperscript{(14)(15)}

Transoral robotic assisted tongue base mucosectomy (TBM) has emerged as a novel management strategy to further reduce the number of patients classified as CUP\textsuperscript{(2)}. The improved vision and manoeuvrability of the robotic instruments allows comprehensive sampling of the tongue base mucosa in a way that has not been previously possible. To date all of the studies have been from North American Institutions. This is the first study to report the UK experience for this technique from three centres that are early adopters of transoral robotic surgery.
Design, Material and Methods

This is a prospective multicentre cohort study. Patients presenting with metastatic HNSCC in a neck node and classified as CUP were offered TBM as a diagnostic intervention at three tertiary head and neck cancer centres (London, Newcastle and Oxford) between 2014 and 2016. While there was some variation in the pathway, only patients in whom sequential clinical, radiological and examination under anaesthesia and biopsies did not identify a primary tumour. All patients underwent PET-CT examination prior to surgical intervention.

All patients underwent comprehensive examination under anaesthesia, followed by a tonsillectomy if appropriate and a TBM. Based on the diagnostic pathway at each centre, driven primarily by logistics of robotic availability, patients underwent tonsillectomy at the same operation or at a later date. The patient cohort in whom diagnostic efficacy of TBM was calculated included only those in whom no primary tumour was identified following clinical examination, imaging including PET-CT and a tonsillectomy with or without biopsies. Patients in whom a primary tumour was identified in the tonsil, even if they underwent a concurrent TBM, have been excluded from this study.

The procedure was performed under general anaesthesia. The da Vinci S was used in OX, the da Vinci S and Si systems were used based on robotic availability at NuTH and ** in SGH. In all cases, the 5mm monopolar spatula cautery was used to perform the dissection, with the 5mm Maryland forceps was used for retraction. The TBM specimen was bisected and orientated before being sent for pathological examination. Figure 1
Results

Across the three centres, 35 TBM were performed in the time period. In three patients SCC was confirmed in the palatine tonsils. These three patients underwent synchronous TBM and palatine tonsillectomy and were excluded from this analysis as these patients would have been identified using conventional techniques. Of the 32 patients who form the subject of this report, the number of patients at each site is as follows: Oxford University Hospital (OUH; n=11), Newcastle upon Tyne Hospitals NHS Trust (NuTH; n=12) and St Georges University Hospital (SGH; n=9). The sex distribution of this cohort was 27 male and 5 female patients with a mean age of 57 years (range, 41 - 74 years).

SCC was confirmed after fine needle aspiration cytology in 23/32 patients. Table 1.

Of the 32 patients, 27 patients underwent a tonsillectomy concurrently or prior to TBM; Four patients had undergone a tonsillectomy as a child and in these patients the tonsillar fossa was rigorously inspected. One patient did not undergo tonsillectomy prior to TBM. 13 patients underwent additional 'blind' biopsies from their upper aerodigestive tract.

The primary tumour site was identified in the lingual tonsil in 53% (n=17) of patients. In 15 patients the tumour was in the ipsilateral tongue base (88%) while in two cases (12%) the tumour was located in contralateral tongue base.

The diagnostic 'hit rate' varied between centres (OUH 45%) NuTH (42%) and SGH (77%).

23/32 (72%) patients were deemed to be HPV positive based in p16 immunohistochemistry, 26% (8) were negative and 1 (3%) was not reported.

Complications were reported in 3 (9%) patients: one patient developed post-operative chest infection and 2 others had post-operative bleeding that settled with conservative treatment. The duration of hospital stay was not reported in all cases.

Discussion
Head and neck cancer represents 6th most common cancer in the world with an estimated 600,000 cases per year. Worldwide the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has increased with the largest increase in western populations and younger men. In the UK over the last 2 decades the incidence has increased from 2.9 per 100,000 males in 1992 to 3.5 per 100,000 in 2010.

The rising incidence of OPSCC is attributed to an increasing role of human papillomavirus (HPV). Evidence suggests that HPV-positive OPSCC may represent a distinct disease entity, tending to occur in a younger patient group, with an improved treatment response and survival when compared to HPV-negative disease.

The ability to identify the primary tumour site has advantages for the patient in terms of understanding their diagnosis and overall survival. It also has advantages for the clinician as treating the site of the primary tumour and likely nodal basin is the basis of head and neck cancer care. Furthermore, ipsilateral rather than bilateral neck and mucosal radiotherapy has a significant beneficial impact on long-term function in particular with respect to swallowing and saliva function. It is also recognised that radiotherapy to the neck increases the risk of carotid artery atherosclerosis and therefore as the patient demographics change long-term functional outcomes become increasingly important.

Strategies to improve identification of the primary site have been evolving for a number of years. The increasing sensitivity and specificity of current imaging techniques has improved. PET-CT appears to offer the highest sensitivity and specificity compared to CT alone or MR scanning and is recommended in the 2016 NICE guidelines. However, it is recognised that the lowest sensitivity for PET-CT is in the tongue base, reflecting the small volume of disease in occult cases and the surrounding uptake of radio-labelled isotope in the surrounding lingual tonsils.
Dissection of the lingual tonsil (laser tongue base mucosectomy) has been reported using the laser with diagnostic identification of the primary site ranging from 75-89%. However the improved visualisation afforded by the robotic assisted technique combined with the limitations of access and line of sight operating with the laser limit this option to a smaller subset of patients[21].

The use of robotic assisted tongue base mucosectomy has been incorporated into a number of differing investigative pathways. Mehta et al[22] report a retrospective series of 10 cases in which they performed a TBM after imaging, CT, MR or PET-CT followed by endoscopy and bilateral tonsillectomy. In this series 9/10 (90%) of cases a primary tumour was identified in the base of tongue.

Patel et al[23] report a retrospective series of 47 patients. CUP was defined after imaging, USS CT MR or PET-CT. 57% of patients only underwent a PET-CT. TBM was combined with a variety of procedures and they report the primary site was identified in 72% of cases. While the majority was in the base of tongue 13 tumours were identified in the tonsil.

Durmus et al[22] report a series of 22 prospective cases. CUP was defined after clinical examination and PET-CT. They carried out frozen section biopsies and only proceeded to a diagnostic palatine and lingual tonsillectomy when they were negative. In this series they identified a primary tumour in 78% of cases the majority in the palatine tonsils.

The sensitivity and specificity of TBM reflects in part the investigations that have been performed prior to the procedure, as these will have diagnosed or raised the suspicion for the site of the primary in a number of cases. A recent systematic review on identifying the unknown primary by Fu et al[8] has reported on 8 studies with 139 patients. Overall this review reported that 80% of the unknown primaries were identified. In the subset of patients in whom physical examination, direct visual examination and imaging were all unremarkable there were 13/22 (59%) primary tumours identified. The majority on the ipsilateral tongue base (96%) while 6% were in the contralateral
tongue base. This systematic review included patients from only North American institutions and yet yields very similar diagnostic rates to this study.

Fu et al report an overall 7% complication rate with post-operative bleeding the most common complication. The slightly higher rate reported in this study may reflect the later adoption of the technique in the UK compared to North America. While not measured directly swallowing function has been reported to recover over around 6 weeks (24) and in the study by Fu et al only 1% did not return to a normal diet. It is yet to be demonstrated that identifying the primary tumour will alter survival and functional outcomes as adjuvant treatment can be tailored to the individual patient. However the ability to treat a unilateral area may have significant affects on swallowing in the long term.

Finally it is likely that the discovery of a primary tumour in a TBM specimen is dependent on pathology laboratory protocols. It is conceivable that systematic examination of all the tissue using a step serial section approach, similar to sentinel node examination, may increase the rate of primary tumour detection(25). This suggestion would require additional pathology resources and costs, but if effective, has the potential to influence patient care.

Conclusion

This study provides further support for the use of tongue base mucosectomy in identifying the primary tumour site. This is the first study outside of North America to report on the sensitivity of the procedure and demonstrates very similar diagnostic rates. Given the relative rarity of the disease it may not be practical to perform a randomised control trial exploring survival and functional outcomes for different treatment strategies. However the use of tongue base mucosectomy should be further explored as this reflects a further refinement in selecting appropriate care for these patients.
Table 1. Investigations performed prior to tongue base mucosectomy:

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Fine Needle Aspiration Biopsy</th>
<th>Core Biopsy</th>
<th>Open Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory investigation of the neck lymph node</td>
<td>23</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Imaging undertaken</td>
<td>MRI</td>
<td>CT</td>
<td>PET-CT</td>
</tr>
<tr>
<td>Tonsillectomy and biopsies of the upper aerodigestive tract</td>
<td>27 (4 patients had a tonsillectomy as a child)</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>