

Main Article

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Transoral robotic tongue base mucosectomy for head and neck cancer of unknown primary: six-year outcome experience

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Abstract

Background and Objective. Head and neck carcinoma of unknown primary is a diagnostic dilemma. The clinical and imaging workup remains ineffective in two-thirds of patients. Transoral robotic surgery has shown an advantage in the primary detection over the previous standard panendoscopy.

Methods. This is an observational cohort study that took place at a large healthcare centre with robotic surgery experience in head and neck over six-years. All included carcinoma of unknown primary patients followed the standard recommendation for primary identification. Final diagnostic step of robotic tongue base mucosectomy with or without tonsillectomy was introduced. The cancer detection rate in tongue base only, the functional outcome and the effect on the cancer pathway were evaluated.

Results. Carcinoma of unknown primary was reported in 44 per cent of patients. All identified specimens were human papillomavirus positive. There was no significant effect on functional outcome of swallowing and the national 62-day cancer pathway. Robotic surgery allowed optimum treatment of carcinoma of unknown primary in early nodal disease.

Conclusion. Robotic surgery is a useful paradigm in the management of carcinoma of unknown primary. It is safe with minimal morbidity and good functional outcome after the surgery.

Introduction

Metastatic cancer of unknown primary in the head and neck constitutes 2–5 per cent of all cases and presents diagnostic and therapeutic challenges.¹ Numerous strategies have been developed to aid in the identification of the primary site.¹ The traditional diagnostic workup for patients with carcinoma of unknown primary in the head and neck includes a detailed clinical history, a comprehensive physical examination including flexible nasolaryngoscopy, and cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI).^{2,3} Fine needle aspiration cytology (FNAC) from the cervical node includes p16 as a surrogate marker to human papillomavirus (HPV) status for a primary in the oropharynx and Epstein–Barr virus to correlate to nasopharyngeal area.³ If these investigations did not reveal the primary, then a panendoscopy under general anaesthesia was performed. Panendoscopy includes an endoscopic examination of the upper aerodigestive tract with blind biopsies of the nasopharynx, tongue base, and pyriform fossae with palatine tonsillectomy.²

The National Institute for Health and Care Excellence in the UK incorporated positron emission tomography CT (PET–CT) in 2016 to assess carcinoma of unknown primary before panendoscopy.^{3,4} Studies have shown that PET–CT can improve the detection of unknown primary tumours in the head and neck by up to 30 per cent, with a sensitivity and specificity of 97 per cent and 68 per cent, respectively.^{5,6} However, PET–CT has a limited capacity to detect sub-centimetre tumours in the oropharynx and has a high rate of false positives.^{6,7} This is particularly pertinent since the oropharynx remains the most common site of carcinoma of unknown primary, especially in patients with HPV-positive disease.^{2,8,9} Thus, alternative diagnostic techniques have been sought to overcome these limitations of PET–CT to reduce the number of patients classified as having cancer of unknown primary.

Transoral robotic surgery for tongue base mucosectomy has recently emerged as a novel diagnostic strategy used in managing carcinoma of unknown primary in the head and neck due to its enhanced three-dimensional visualisation of the oropharynx structures.¹ This procedure involves removing the mucosa with the lymphatic tissue from the base of the tongue while preserving the underlying musculature.^{10,11} The specimen is analysed by serial sectioning.¹² Studies using a transoral robotic surgery approach reported high detection rates (77–90 per cent). These studies, however, usually include tumours detected from transoral robotic assisted palatine tonsillectomy.^{2,11,13}

It may be argued that adding this additional step to the diagnostic process could affect cancer's waiting time, leading to a potential delay in definitive treatment. Thus, this may affect compliance with the National Health Service England national cancer waiting pathway (e.g., cancer patients should be treated within 31 days after the decision to treat) that recommended 94 per cent target.⁹

Thus, this study aims to demonstrate our local detection rates of primary tumours in patients with metastatic cervical adenopathy from an unknown primary using robotic tongue base mucosectomy. In addition, we also aim to assess the effect of this diagnostic tool on the national cancer waiting time target.

Material and methods

Study design

The present study is a Cohort observational single-centre retrospective review of patients with head and neck cancers of unknown origin. From January 2016 to June 2021, patients underwent transoral robotic surgery at the University Hospitals of Derby and Burton. Patients had either an ultrasound-guided needle aspiration or a core biopsy of their cervical lymphadenopathy to confirm a metastatic neck squamous cell carcinoma; p16-immunohistochemistry testing served as a surrogate for HPV status.

Inclusion and exclusion criteria

The study included only patients in whom comprehensive physical examinations, including flexible nasolaryngoscopy, imaging (MRI or CT), and PET-CT, failed to identify a primary mucosal site in the upper aerodigestive tract. All patients had undergone PET-CT scans as part of their diagnostic workup. We excluded patients whose PET-CT scans showed low nonspecific fluoro-deoxy-glucose (FDG) avidities at anatomical sites that later confirmed to be the primary tumour site on histology. Furthermore, patients diagnosed with primary palatine tonsil tumour following a combined transoral robotic tongue base mucosectomy and palatine tonsillectomy were excluded from the study. Such primaries could have been identified using conventional methods.

Data extraction and statistical analysis

We retrospectively analysed the following data from the patient's records: basic patient demographics, smoking status, history of prior palatine tonsillectomy, method of diagnosis (ultrasonic-guided FNAC or core biopsy), p16-immunohistochemistry status, the extent of transoral robotic surgery resection, site and size of the primary tumour when discovered, and the pathological tumour-node-metastasis (TNM) stage according to the American Joint Committee on Cancer, 7th Edition.¹⁴

Furthermore, we analysed the length of hospital stays following a surgery, the swallowing function outcome using the International Dysphagia Diet Standardisation Initiative, 2019 (<https://iddsi.org/framework/>), complications, and the definitive oncology treatment modality. Referral patterns and cancer waiting times were also assessed, particularly from diagnosis to receiving definitive treatment.

The collected data were analysed using SPSS version 25 for Windows (SPSS Inc., Chicago, IL). The Fisher's exact test was used to determine statistical significance.

Material

The da Vinci Si and X systems (3 arms) (Intuitive Systems, Sunnyvale, CA) were used. In all cases, the 8 mm monopolar spatula cautery was used to perform the dissection, and the 5 mm Maryland forceps were used for retraction. Tongue base mucosectomy specimens were oriented before being sent for pathological examination. The project used anonymised data for benchmarking carcinoma of unknown primary reduction rate for service improvement, hence ethics approval was not required.

Results

Nineteen patients underwent transoral robotic surgery for carcinoma of unknown primary during the study period. All patients underwent a clinical history and physical examination, including flexible nasolaryngoscopy, with no clinical evidence of primary tumour in an outpatient setting. As part of their diagnostic evaluation, all patients had conventional imaging (MRI/CT) and PET-CT scanning. In one patient, however, PET-CT imaging revealed low nonspecific fluoro-deoxy-glucose (FDG) avidity at the base of the tongue that corresponded to the primary tumour site. The patient was therefore excluded from the study. Two additional patients who had undergone combined transoral robotic tongue base mucosectomy and tonsillectomy where malignancy was detected in the palatine tonsils also were excluded from the study as per inclusion criteria.

Consequently, 16 patients who met all inclusion criteria were included (Figure 1). The diagnosis of carcinoma of unknown primary was made after ultrasound-guided FNAC of the cervical lymph node in 15 out of the 16 patients (94 per cent) and core biopsy in one patient (6 per cent) because the initial ultrasound-guided FNAC was inconclusive.

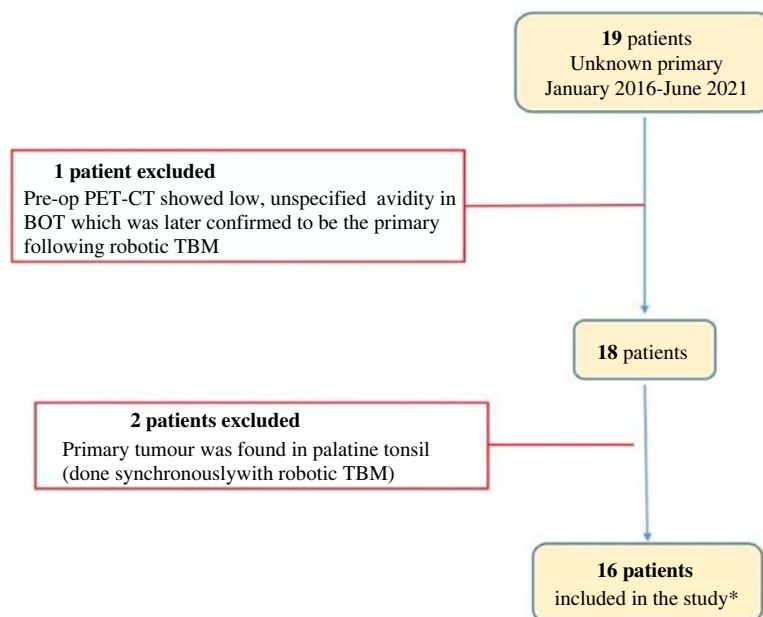
The immunohistochemistry for p16 was positive in 14 of 16 patients (87.5 per cent) and negative in two patients (12.5 per cent). One patient underwent bilateral palatine tonsillectomy as a child. Table 1 indicates the demographic characteristics of patients. The average age of these patients was 57 years, with 13 male (81 per cent) and three female (19 per cent) patients. Concerning smoking history, six patients (37.5 per cent) had never smoked and were all p16 positive. Four patients (25 per cent) were current smokers, while six patients (37.5 per cent) were ex-smokers.

All patients underwent transoral robotic tongue base mucosectomy. Ten patients (62.5 per cent) had diagnostic transoral robotic tongue base mucosectomy without neck dissection. Previously, these patients had undergone conventional diagnostic panendoscopy of the upper aerodigestive tract with palatine tonsillectomy and concurrent neck dissection. Six patients (37.5 per cent) underwent panendoscopy, synchronous transoral robotic surgery-assisted palatine tonsillectomy, tongue base mucosectomy and neck dissection.

According to the American Joint Committee on Cancer, 7th Edition,¹⁴ six patients (37.5 per cent) had nodal status N1, four patients (25 per cent) had nodal status N2a, five patients (31.2 per cent) had nodal status N2b, and one patient (6.3 per cent) had nodal status N3. In seven patients, the definitive histology after neck dissection revealed extracapsular spread (Table 2).

Results of robotic tongue base mucosectomy

The final histopathology analysis identified primary tumour sites in seven of the 16 patients (44 per cent). All identified



BOT: Base of tongue, TBM: Tongue base mucosectomy.

* All the patients had negative physical examinations and negative imaging (CT/MRI) and PET-CT

Figure 1. Study scheme.

tumours were T1 with a mean size of 5.9 mm. As shown in Table 1, six of seven (86 per cent) cancer-positive specimens measure less than 1 cm in size, and one specimen measured just 1.1 cm. Furthermore, six of the seven patients (86 per cent) had a tumour in the ipsilateral tongue base. In contrast, one patient (14 per cent) had a tumour in the contralateral tongue base to the cervical node with metastatic carcinoma. A second-look robotic transoral tongue base mucosectomy was necessary for two of the seven patients (28 per cent) due to the involvement of the deep margins. Histologically, both patients had negative second-look results. As a result of a noteworthy observation, all seven patients with primary identified through robotic tongue base mucosectomy were p16 positive. However, the association between p16 status and successful results of tongue base mucosectomy with transoral robotic surgery was not statistically significant ($p = 0.475$).

Hospital stay length and adverse events

The average length of hospital stay was 1.5 days. The 10 patients (62.5 per cent) who underwent the diagnostic transoral robotic surgery without neck dissection stayed for only one day. Two of the six patients (33 per cent) who underwent panendoscopy with transoral robotic surgery-assisted palatine tonsillectomy and tongue base mucosectomy and simultaneous neck dissection stayed for three days after the operation. On the other hand, the remaining four of the six patients (67 per cent) required two days of hospitalisation. The patients in our series did not experience any significant intra-operative or post-operative bleeding. One patient was readmitted one week after surgery for pain management.

The cancer waiting time

In this study, 10 out of 16 patients (62.5 per cent) were referred for suspected head and neck cancer via the two-week wait pathway, while six patients (37.5 per cent) were referred otherwise (e.g., urgent referrals from general practitioners or

other services such as accident and emergency). Notably, regardless of the referral pathways, 14 patients (87.5 per cent) were treated within 31 days of the decision to pursue treatment. Two patients (12.5 per cent) exceeded the 31-day limit. These patients started definitive treatment on days 35 and 37 from the diagnosis. The Fisher's exact test compared to national target (94 per cent) was not significant (p -value = 1 at $p < 0.05$).

Oncological adjuvant treatment

Six patients (37 per cent) whose final histologies were N1 with no extracapsular spread did not require further treatment. It should be noted that the primary was detected in two of the six patients (33 per cent) with N1. The tumour was staged as T1. Therefore, it may be argued that these two patients would have received suboptimal treatment if transoral robotic surgery had not been performed.

Table 3 shows that five patients with detected primary tumours required adjuvant radiation therapy, four of these five patients also received concurrent chemotherapy treatment. Nevertheless, it is essential to note that these patients received a reduced radiation field compared to the wide-field radiation they would have received without transoral robotic surgery. Moreover, chemotherapy was necessary due to extracapsular spread in the lymph nodes rather than positive margins at the primary tumour site.

Swallow outcomes

Four patients (25 per cent) did not tolerate a normal diet in the immediate post-operative hospital stay. Three of these four patients required level 6, 5 and 4 diets (International Dysphagia Diet Standardisation Initiative 2019, <https://iddsi.org/framework/>) and one patient required a nasogastric tube for one day only. At six months, six patients were still on a modified diet (two on level 6 and four on level 5). The four patients on level 5 diets and one patient on level 6 diet had post-operative radiotherapy. At one year after surgery, there

Table 1. Patients' demographics, p16 status, and American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) 7th Edition¹⁴

Gender	Age	Smoking Status	p16 Status	Pathological TNM (7th Edn.)	Extra-capsular Spread	Tumour Site	Tumour Size	Margins (primary site)	Adjuvant treatments
M	43	Never smoked	Positive	T1 N1	No	Ipsilateral BOT	7 mm	Positive deep margin*	No
M	50	Ex-smoker	Positive	T0 N2b	Yes	Unknown	—	—	CRT
M	58	Smoker	Negative	T0 N2b	Yes	Unknown	—	—	CRT
M**	63	Never smoked	Positive	T1 N1	No	Ipsilateral BOT	2 mm	Negative margins	No
M	61	Never smoked	Positive	T0 N2a	No	Unknown	—	—	RT only
M	61	Ex-smoker	Positive	T1 N2b	No	Contralateral BOT	9 mm	Negative margins	RT only
M	63	Smoker	Positive	T1 N3	Yes	Ipsilateral BOT	11 mm	Positive deep margin*	CRT
F	53	Ex-smoker	Positive	T1 N2b	Yes	Ipsilateral BOT	4 mm	Negative margins	CRT
F	58	Ex-smoker	Positive	T0 N1	No	Unknown	—	—	No
M	57	Never smoked	positive	T1 N2a	Yes	Ipsilateral BOT	3 mm	Negative margins	CRT
M	53	Never smoked	Positive	T0 N2b	No	Unknown	—	—	RT only
M	58	Smoker	Negative	T0 N2a	Yes	Unknown	—	—	CRT
F	54	Smoker	Positive	T1 N2a	Yes	Ipsilateral BOT	5 mm	Negative margins	CRT
M	51	Ex-smoker	Positive	T0 N1	No	Unknown	—	—	No
M	60	Never smoked	Positive	T0 N1	No	Unknown	—	—	No
M	70	Ex-smoker	Positive	T0 N1	No	Unknown	—	—	No

*Underwent second-look transoral robotic surgery re-resection with negative histology. **Previous palatine tonsillectomy as a child. CRT: Chemoradiation. RT: radiation. BOT: Base of tongue.

Table 2. Nodal staging according to the American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) 7th and AJCC/UICC (Union for International Cancer Control) 8th Editions^{14,15}

Nodal stage (7th TNM)	Number of patients (%)	Number of cases with extracapsular spread	p-Nodal stage (8th TNM) HPV+ve	p-Nodal stage (8th TNM) HPV+ve
N1	6 (37.5%)	0	N1 = 11	N2a = 1
N2a	4 (25%)	3	N2 = 3	N3b = 1
N2b	5 (31.2%)	3		
N3	1 (6.3%)	1		
Total	16	7	14	2

p-Nodal stage = pathologically confirmed nodal stage. HPV+: Human Papilloma virus positive

Table 3. Distribution of adjuvant oncological therapy

	Detected Primary Tumour Group	Undetected Primary Tumour Group
Number of patients	7	9
Adjuvant therapy		
– None	2	4
– Radiation alone	1	2
– Chemoradiation	4	3

was one patient who required a level 6 diet (improved from level 5 diet at six months). No patient needed a gastrostomy feeding tube.

Discussion

This study examined the role of transoral robotic surgery tongue base mucosectomy in identifying a primary tumour in patients presenting with metastatic cervical lymphadenopathy of unknown origin. In a cohort of 16 patients who met all eligibility criteria, our study revealed a 44 per cent detection rate. A recent systematic review of 21 studies (556 cases) found wide variations in the detection rate (53–91 per cent) of a transoral robotic surgery approach to identify the primary among the reviewed studies.¹⁶ There may be reasons for the wide variation in success rates, such as the quality and size of the studies and the large variation in the diagnostic workup. For example, some studies did not indicate whether patients had any suspicious findings in investigations (e.g., low and unspecific PET–CT avidity at the base of the tongue before surgery).¹⁶ In addition, other studies had reported success rates in identifying primary cancers, including those detected during transoral robotic surgery-assisted palatine tonsillectomies.^{2,11} In this regard, we found that the cancer detection rate in Mistry *et al.*¹¹ was 43 per cent (12/28 patients) when we eliminated cancers found in palatine tonsils.

It should be noted that all tumours identified had T1 stage ranging from 2–11 mm. The small size of the identified tumours with tongue base mucosectomy may explain the negative PET–CT results.^{5,6} Therefore, this illustrates the additional benefits of adding the transoral robotic surgery tongue

base mucosectomy in the workup for carcinoma of unknown primary in the head and neck.

One of the seven patients (14 per cent) with identified primary tumours had their primary tumour located in the contralateral tongue base to the metastatic cervical nodes. Similar to our findings, other studies have reported 12 per cent detection rate of contralateral primary tongue base tumors.^{1,8} In light of this, it may be more appropriate to perform a bilateral tongue base mucosectomy.

Transoral robotic surgery tongue base mucosectomy is primarily performed for diagnostic purposes. Thus, we did not focus on achieving clear margins. The reason for this is that these tumours typically are not visible during surgery. However, five of the seven (72 per cent) detected primary cancers were resected with clear margins, and two of the seven (28 per cent) detected primary cancers required a second transoral robotic surgery resection to achieve negative margins. In this regard, it could be argued that transoral robotic surgery tongue base mucosectomy may also serve as a therapeutic procedure.¹¹

It is noteworthy that if radiotherapy was indicated, a narrower radiation field was applied rather than the wider radiation field that would have been used if primary cancer had not been detected.^{8,17} By reducing the radiation field, potential morbidity associated with the treatment is minimised.^{13,17} Detecting primary cancer in patients with N1 diseases was of paramount importance. The management of carcinoma of unknown primary with small nodal disease (N1) and no extracapsular spread after neck dissection is currently based on close clinical monitoring.^{3,18} As a result of our study, we identified the primary tumour in one-third of patients (two out of six) with N1 disease. Without transoral robotic surgery, the primary tumour site would have remained untreated in these two patients, resulting in a sub-optimal oncological treatment.

The primary tumours identified in our series were all p16 positive (HPV-related oropharyngeal cancers). Thus, we detected the primary tumour in seven out of fourteen (50 per cent) p16-positive carcinoma of unknown primary, but not in any of the p16-negative carcinoma of unknown primary. While we acknowledge the small size of our study (only two patients were p16 negative), our results may be consistent with increasing evidence in the literature that suggests transoral robotic surgery has a low success rate of transoral robotic surgery tongue base mucosectomy in detecting the primary cancer in HPV-negative nodal disease.¹⁹ Thus, in such cases, a transoral robotic surgery tongue base mucosectomy may not be necessary, particularly if it delays definitive oncological treatment.²⁰

- Transoral robotic surgery-assisted tongue base mucosectomy improves primary site identification in head and neck carcinoma of unknown primary cases
- Transoral robotic surgery-assisted tongue base mucosectomy is highly effective in cases of HPV-positive carcinoma of unknown primary
- Transoral robotic surgery-assisted tongue base mucosectomy may not be necessary in patients with HPV-negative carcinoma of unknown primary, especially if it would delay definitive oncological treatment
- Increasing accessibility to robots for head and neck procedures is being advocated where one-stage procedures are feasible
- Overall, transoral robotic surgery-assisted tongue base mucosectomy does not significantly delay definitive oncological treatment

Access to robotic technology was endorsed by our health-care centre to streamline its service. The combined diagnostic

transoral robotic surgery and the neck dissection into a single-stage procedure reduced hospital admissions. Furthermore, the enhanced recovery after the procedure was shown with the restoration of normal oral diet in 75 per cent of the patients immediately post-operative and the discharge of all patients within 2–3 days. One could argue that increasing access to robots could improve utilisation of theatre schedules, admission rate and overall service reimbursement without significant delay in cancer treatment. However, further cost-analysis studies are required to test it.

It is worth mentioning that a temporary deterioration of swallowing was observed in the first 3–6 months following surgery in 37.5 per cent (6 of 16) of patients; of whom 31 per cent (5 of 16) required postoperative adjuvant treatment. However, no patient needed a gastrostomy feeding tube, confirming the limited morbidity related to robotic tongue base mucosectomy.

This is the first study to examine the effect of transoral robotic surgery-assisted tongue base mucosectomy on compliance with the recommended cancer waiting times. Since not all patients were referred under the two-week wait suspected head and neck cancer pathway, we analysed the results according to the recommended 31-day target period (from decision to treat to starting definitive treatment). Within 31 days of their cancer diagnosis, 14 of 16 patients (87.5 per cent) received definitive oncological treatment. Two patients breached the 31-day deadline by only one week (day 35 and day 37). Therefore, we support incorporating transoral robotic surgery tongue base mucosectomy into the carcinoma of unknown primary pathway without significant delays in definitive oncological treatment. Our data are primarily from retrospective reviews of case series from one centre, therefore prospective and multi-centre studies on long-term oncological outcomes and cost effectiveness are much needed.

Conclusion

Transoral robotic surgery assisted tongue base mucosectomy improves primary site identification in head and neck carcinoma of unknown primary cases. It is highly effective in cases of HPV-positive carcinoma of unknown primary. However, it may not be necessary in patients with HPV-negative carcinoma of unknown primary, especially if it would delay definitive oncological treatment. Robotic head and neck procedures are being advocated where one-stage procedures are feasible.

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Competing interest. None declared.

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