

# Royal Society of Medicine Surgical Innovation Day Adrian Tanner Prize Winner 2019: Multidisciplinary care and surgical innovation for the benefit of the patient with head and neck cancer of unknown primary

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## Lesson

Head and neck carcinoma of unknown primary accounts for approximately 1–5% of all head and neck cancers and presents a genuine diagnostic and therapeutic dilemma. Despite advanced investigations, the primary tumour location remains unknown in up to 40% of these cases. Transoral robotic surgery presents a viable diagnostic and therapeutic option in these patients. This surgical innovation alongside advances in the understanding of head and neck cancer biology means that a multidisciplinary approach in the management of these complex patients is of utmost importance to ensure optimal therapeutic outcomes.

## Keywords

surgical innovation, multidisciplinary team, head and neck cancer, transoral robotic surgery, human papilloma virus, ear nose and throat surgery

## Background

Head and neck cancer of unknown primary (HNCUP) accounts for approximately 1–5% of all head and neck cancers and is a genuine diagnostic and therapeutic dilemma.<sup>1</sup> The typical presentation of HNCUP is a patient with a suspicious neck lump that demonstrates metastatic carcinoma on fine needle aspiration cytology (FNAC), but no apparent primary tumour on clinical examination of the mucosal surfaces of the upper aerodigestive tract (UADT) can be found. Despite rigorous investigations in accordance with the British Association of Head and Neck Oncologists (BAHNO) (including Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Positron Emission Tomography-Computed Tomography (PET-CT)), the primary site remains unknown in approximately 40% of cases.<sup>1,2</sup> Identification of the primary tumour is key to reducing morbidity from wide-field radiation effects whilst also increasing overall and disease-free

survival.<sup>3,4</sup> When a primary lesion is identified in these patients, it is commonly located in the tonsils (44.7%) or base of tongue (BOT) (43.9%).<sup>3</sup>

Transoral Robotic Surgery (TORS) is a novel surgical approach with 3D vision, precision and access unparalleled by traditional operative techniques. TORS permits not only identification of a primary lesion but can also be harnessed as a tool for surgical resection. Consequently, a recent meta-analysis credited TORS with an overall oropharyngeal primary diagnostic yield of 74%, whilst specifically for the BOT, a diagnostic yield of 53% in patients where all previous imaging has returned negative.<sup>1</sup>

As reflected in the American Joint Committee on Cancer 8th edition of tumour staging, there is currently significant debate as to the role of high-risk human papilloma virus (HPV) status in the stratification of head and neck cancer patients.<sup>5</sup> p16 is used commonly as a surrogate marker of HPV infection status, and although sensitivity is approximately 80%, it is the most widely reported tool for HPV infection status.<sup>1,6</sup> As demonstrated by the adapted and simplified Table 1, current literature has demonstrated HPV-positive and HPV-negative head and neck cancer patients differ in multiple aspects.<sup>7</sup>

With the separate staging system comes opportunities for further research into the treatment of oropharyngeal squamous cell carcinoma (SCC) patients as separate entities, reflected by ongoing trials into de-escalation therapy such as Postoperative Adjuvant Treatment for HPV-positive Tumours (PATHOS).<sup>8</sup> Hence, given the rapidly changing head and neck cancer landscape, specialist input evaluating the most up-to-date research is essential to ensure optimal therapy for patients.

Given the diagnostic and therapeutic complexity with these patients, we present a case that illustrates how surgical innovation and multidisciplinary team (MDT) care can combine to optimise the care of a patient with HNCUP.

**Table 1.** Comparison of HPV-positive and HPV-negative head and neck cancer patients.

Feature	HPV-positive head and neck cancer	HPV-negative head and neck cancer
Age (mean)	Younger (40–60)	Older (>60)
Male:Female ratio	8:1	3:1
Socioeconomic status	Higher	Lower
Risk factors	Nine subtypes of HPV	Alcohol, smoking, betel nut chewing
Anatomical sites	Oropharynx	All sites
p16 gene product	Overexpressed	Usually not evident
Regional lymph node involvement	Early, bulky	Later
3-year overall survival (months)	82.4% (95% CI: 77.2–87.6)	57.1% (95% CI: 48.1–66.1)
Overall response to treatment	94% (95% CI: 87–100)	58% (95% CI: 49–74)

## Case presentation

A 64-year-old bus driver presented to the Ear, Nose and Throat (ENT) Head and Neck clinic with an eight-week history of a left-sided neck mass, which he had detected whilst shaving. He was otherwise fit and well, and had no systemic symptoms.

Medical history included type 2 diabetes, high cholesterol, hypertension and previous palatine tonsillectomy (for recurrent infections) in childhood. The patient was a lifelong non-smoker and reported only occasional alcohol intake.

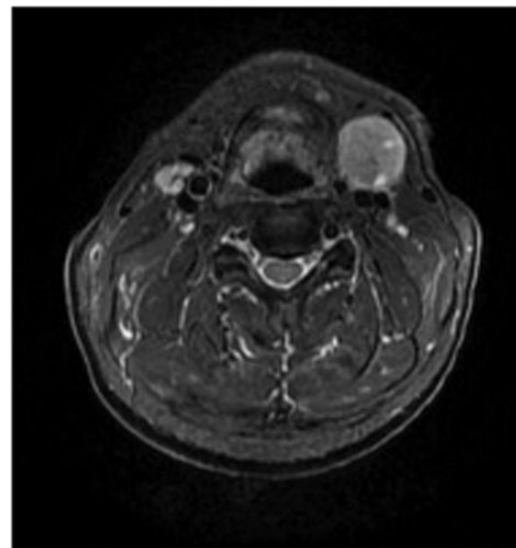
On examination, palpation revealed a firm non-tender 2 cm left level II neck lymph node. There was no other associated cervical lymphadenopathy. Flexible nasoendoscopy of the larynx, base of tongue, vallecula and pyriform fossae revealed no mass and no mucosal abnormality.

The patient was investigated according to BAHNO and National Institute of Clinical Excellence (NICE) guidance. Ultrasound (US)-guided FNAC revealed a 2 cm level II neck lymph node that was metastatic SCC and p16 negative. MRI neck with contrast and 18-fluoro-deoxyglucose (FDG) PET-CT did not identify a primary tumour site (Figure 1).

HNCUP was determined by strict criteria and head and neck MDT agreement: metastatic neck carcinoma confirmed on cytology, negative clinical examination and endoscopy, and negative imaging for primary (US/MRI/PET-CT). Consequently, the patient was staged as T0 N2a M0 SCC.

The patient was listed for a panendoscopy (systematic examination of all the mucosal surfaces of the head and neck under anaesthetic), robotic tongue base mucosectomy and dental extractions.

**Figure 1.** Axial view of MRI neck scan with contrast identifying a pathological left level II lymph node. No obvious UADT primary lesion was visible.



The patient underwent the procedure 17 days from initial presentation and there were no intra-operative or post-operative complications. With key speech and language (SALT) and dietician input, the patient resumed normal oral intake within 24 h and was discharged the next day.

Histology obtained from this procedure revealed a 9-mm primary poorly differentiated SCC within the left lingual tonsil which was p16 positive. The

margins were <5 mm. The patient's staging was updated to T1N2a M0.

In a joint clinic involving the oncologist, MacMillan cancer nurse specialist and Head and Neck surgeon, a decision was made in partnership with the patient to progress with a further robotic tongue base resection with bilateral selective neck dissection (levels II–IV) followed by adjuvant radiotherapy as required.

In preparation for this second procedure, the patient underwent an allied health professional (AHP) MDT including the SALT and dieticians to ensure enhanced recovery via pre-operative optimisation and peri-/post-operative nutrition planning. The patient underwent the procedure, which was uncomplicated, and returned to normal oral intake before discharge seven days post-operatively.

On subsequent histological analysis, the primary tumour was excised with clear margins as no residual disease was identified. The left neck dissection yielded 34 lymph nodes of which two were positive for metastatic SCC, and the right neck dissection was negative for disease in all lymph nodes. The patient was re-staged as pT1N2b M0 p16 positive left base of tongue SCC. After discussion in the joint oncology and ENT Head and Neck clinic regarding the evidence for de-escalating adjuvant therapy in HPV positive patients, the decision was made in partnership with the patient to complete his treatment with post-operative left neck and oropharynx radiotherapy at levels Ib to V (60Gy/30 fractions).

Less than five months from initial presentation, the patient completed his course of radiotherapy with minimal levels of morbidity (suffering transient grade 2 mucositis and unilateral otitis media with effusion, both of which resolved without intervention).

At the latest follow-up one year since initial presentation, the patient had no signs of recurrence on clinical examination and demonstrated excellent treatment response on a follow-up PET scan. The patient has been discharged from dietician follow-up. He is also almost back to pre-treatment functional status by returning to working three days a week. He has a normal oral intake and his weight is stable.

## Discussion

There were three specific points of impact due to surgical innovation that influenced this case. The first TORS procedure was able to identify a previously unidentifiable 9 mm primary lesion. The second TORS procedure alongside bilateral neck dissection allowed complete excision of the primary lesion whilst also allowing staging of the contralateral neck for the

presence or absence of disease. In doing so, it allowed targeted radiation to the ipsilateral neck and oropharynx only and thus reduced radiation-associated morbidity.

Malignant metastases in level II is a hallmark of HPV-related SCC usually with sub-clinical primaries in the oropharynx.<sup>2</sup> The Head and Neck Cancer United Kingdom (UK) National Multidisciplinary Guidelines recommend all patients presenting with confirmed cervical lymph node metastatic SCC and no apparent primary should undergo bilateral tonsillectomy, PET-CT as well as panendoscopy and directed biopsies.<sup>2,9</sup> However, literature suggests PET-CT provides additional primary tumour detection rates in HNCUP over conventional imaging techniques in 37–44% of cases with a sensitivity and specificity of 97% and 68%, respectively.<sup>10</sup> Specifically, data suggest identification of sub-centimetre lesions is of particular difficulty (and in this case the lesion being 9 mm). Consequently, TORS provides a useful adjunct for Head and Neck surgeons and patients in identifying a primary lesion that is smaller than the resolution offered by PET CT, which can often be the case with HPV-positive patients who experience early metastasis with bulky lymph nodes.<sup>7</sup> Therefore, the UK guidelines advise tongue base mucosectomy where facilities and expertise exist.<sup>2</sup>

Whilst traditional surgical approaches are well established for palatine tonsillectomy, TORS allows unique access to the BOT for precise tongue base mucosectomy/lingual tonsillectomy that otherwise would not be possible with traditional surgical techniques. Transoral Laser Microsurgery (TOLM) is an alternative to TORS with comparable results (primary identification rate for TOLM 91% (85%–98%; 95% CI); however, the most recent meta-analysis of transoral tongue base mucosectomy for HNCUP only demonstrated 17% of patients undergoing TOLM compared to 83% undergoing TORS.<sup>1</sup> Therefore, more data are required in order to fully evaluate the two methods. There are also reported advantages of TORS over TOLM in the literature which includes 3D panoramic vision, improved range of motion, better optics, hand tremor filtration and easier en bloc resection.<sup>11</sup>

Therefore, this case adds to the growing body of literature that TORS is a useful emerging surgical strategy that would permit identification of primary lesions that cannot be seen with conventional diagnostic approaches.<sup>2</sup> TORS in this case also allowed complete excision of the lesion, with very little associated morbidity.

The UK guidelines provide recommendations for N2b HNCUP management, which involves ipsilateral selective or modified radical neck

dissection ± contralateral procedures.<sup>2</sup> It also recommends ipsilateral radiotherapy for these patients with the consideration of bilateral procedures and possibly chemotherapy.<sup>2</sup> In this case, the patient underwent bilateral selective neck dissection with ipsilateral radiotherapy at 60Gy/30 fractions. In doing so, the patient was staged in nodal status bilaterally with sparing of non-nodal structures in neck dissection. In addition, the radiotherapy regime was delivered to the ipsilateral neck only, sparing the patient from immediate and long-term contralateral radiation-associated morbidity. The lack of convincing data that adjuvant chemotherapy is of benefit in disease-free or overall survival therefore resulted in this patient being spared chemotherapy.<sup>2</sup>

This case demonstrates how strict MDT discussion to ensure the correct diagnosis and management plan is formulated in accordance with UK National Guidelines whilst also reducing morbidity for the patient.

Given the current state of clinical equipoise regarding the stratification of HPV-positive and HPV-negative head and neck cancer patients as potentially two separate disease entities, the input of all MDT members in the choice of adjuvant radiotherapy was key. There remains significant debate at present regarding the de-escalation of therapy in HPV-positive patients given the observation of superior outcomes compared to HPV-negative disease of comparable stage. Due to the current lack of positive evidence for de-escalation, and recent literature from the de-escalate and RTOG1016 trials suggesting de-escalation of therapy may be associated with inferior two-year survival and increased recurrence loco-regionally, further research is required.<sup>12,13</sup> From existing knowledge underpinning ongoing research trials such as PATHOS, the decision was made to offer adjuvant treatment to the ipsilateral oropharynx and neck in the regime suggested as per the UK guidelines (60Gy/30 fractions).<sup>2,8</sup> The evolving nature of this aspect in HNCUP care means constant MDT evaluation and discussion of the current literature is key in ensuring care with minimal morbidity but optimal therapy.

Another important point of impact of the MDT was the pre- and peri-operative MDT care to ensure minimal post-operative morbidity and inpatient hospital stay. Imperatively, throughout the patient's pathway the patient was at the centre of all decision-making (as reflected below) through various joint clinics and AHP MDTs. Finally, the coordination of all members of the MDT ensured an efficient pathway for the patient ensuring time from presentation to treatment was within 62 days.

## Patient perspective

I first noticed a lump in my neck when shaving around the middle of June 2018. I decided to wait and see if it was just a swollen gland and hopefully rest and relaxation would see an end to it. When I saw my GP they weren't sure what it was but gave me some antibiotics and an inhaler and suggested that I visit my dentist who referred me under the two-week pathway.

After my ultrasound scan, at the Head and Neck clinic the doctor told me that there was after all a problem – this being cancer of the throat. Awaiting results of further investigations was one of the longest, anxious, stressful weeks of my life. All sorts of thoughts go through your mind, how long have I got to live, has it spread, is it a false alarm, am I just having a bad dream and will it be treatable.

At the follow-up appointment, the consultant explained in detail what had been found. He also explained everything to do with the throat cancer and what the possible treatment plan would entail asking me at each stage if I was happy to follow the suggested route of treatment.

He then said I could go away and think things over – if I was happy there was an opportunity that coming Sunday to proceed with Robotic Surgery. I felt the consultant was very positive about the treatment and the likely outcome – but also felt I still had the opportunity to make the final choice. After both operations, the ENT consultant and members of his team came to see me and let me know how everything had gone which was very reassuring and comforting to know.

My radiotherapy treatment ran for six weeks. I did struggle as it was much worse than I believed it would be. My food intake was very little and the Fortisips and strong painkillers were a godsend. I was also very grateful that my wife could take me to each radiotherapy treatment and I didn't have to use public transport (strange that – as I am a bus driver!).

I must say that throughout my whole experience I have felt that I was treated with respect and kindness by everyone I came into contact with even though this has been a very stressful time for me and my family. You do not realise how many people are involved with all aspects of your care and how grateful you are that they are there.

Finally, I would like to pass on my heartfelt grateful thanks to everyone involved.

## Key message

Advancements in surgical innovation and understanding of head and neck cancer mean a multidisciplinary approach which is key for optimal outcomes.



## Learning points

- Utilisation of surgical innovation alongside the multidisciplinary team was vital in:
  - Patient selection
  - Identification of primary lesion
  - Excision of primary lesion
  - Reduction of radiotherapy and surgical morbidity.
- The evolving field of head and neck cancer with regard to Human Papilloma Virus necessitates strict multidisciplinary approach to evaluate current literature and ensure appropriate therapy.
- Patient-led decision making combined with multidisciplinary team input helps ensure that the patient feels empowered in the decision making for their healthcare.
- The current model and pathway for head and neck cancer patients at this centre can lead to timely assessment and treatment of patients.

## Declarations

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**Guarantor:** RM.

**Contributorship:** RM: Conception, research and design of the case report, presentation at the Royal Society of Medicine Surgical Innovation Day 2019. AW: Guidance throughout write-up and presentation of the case report. NW: First draft of the case report. EO: Guidance throughout and subsequent final approval of the version to be submitted.

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