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Case Study

Oropharyngeal Squamous Cell Carcinoma: HPV as a Driver for Surgical Innovation

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Key Learning Points

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The incidence of oropharyngeal cancer is increasing, with epidemiological and molecular evidence identifying Human Papilloma Virus (HPV) as a causative factor. The incidence of HPV-positive (HPV+) oropharyngeal squamous cell carcinoma (OPSCC) has doubled in the last decade. HPV+ OPSCC affects a different demographic profile to HPV negative (HPV-) disease and also generally has a more favourable prognosis. OPSCC is currently managed typically with radical radiotherapy (+/- chemotherapy) or transoral surgery and neck dissection with adjuvant treatment as necessary depending on the stage of disease. As HPV+ patients are typically younger and have fewer comorbidities, it is vital to investigate the role of new surgical techniques in the treatment of this cancer with the aim of reducing side effects of current treatment regimes.

A 59-year-old man with no co-morbidities presented with a painless lump on the left side of his neck. Imaging and histology revealed a T2N1M0 squamous cell carcinoma of the left palatine tonsil. Left tonsillectomy and neck dissection were performed as part of the PATHOS trial, a multicentre phase III trial for patients with primary OPSCCs that are trans-orally resectable. In this trial, surgery to the primary malignancy is performed with Transoral Laser Microsurgery (TLM) or Transoral Robotic Surgery (TORS), depending on local practice.

Newer techniques such as TLM and TORS offer less invasive surgical approaches to resect OPSCC compared to older, more morbid approaches such as mandibulotomy (splitting and re-joining the jaw). Clinical trials are currently underway to determine whether separate treatment guidelines should be put in place for HPV+ OPSCC, both to de-escalate low risk cancers and escalate treatment for high-risk patients.

Introduction

Squamous cell carcinoma (SCC) accounts for the majority of oropharyngeal cancers and has historically been associated with smoking and alcohol. However, the incidence of HPV-positive oropharyngeal SCC (HPV+ OPSCC) has doubled in the last decade, with the percentage of HPV+ oropharyngeal cancers increasing by 53.7% in 20 years[1]. In comparison to HPV- disease, HPV+ OPSCC patients are younger, more likely to be non-smokers and have fewer comorbidities[2]. Better oncological outcomes have also been demonstrated in patients with HPV+ OPSCC[3]. With this altered profile of OPSCC emerging, there has been a renewed interest in the management of this cancer.

Traditionally, oropharyngeal cancers were treated with open surgery due to the anatomical intricacy surrounding the oropharynx. However, due to the high risk of post-operative complications and the development of functional morbidities, chemoradiation became increasingly popular in the late 20th century. Efficacy of this treatment is high, with this therapy still being the standard of care today. Although the use of this treatment is highly favoured in the medical community, adverse effects include dysphagia, dry mouth, and sticky saliva[4]. Moreover, complications from long-term toxicity have been found to be relatively common[5], highlighting the limitations of chemoradiation in the treatment of OPSCC. New surgical approaches are changing the treatment of OSPCC. Minimally invasive surgical, techniques such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) offer outcomes associated with a decreased rate of functional morbidities[6].

There is currently no difference in treatment guidelines between HPV+ and HPV- OPSCC. HPV status is considered in terms of clinical trial eligibility; however, it does not have an impact on treatment modality. Given the

altered patient demographic and advances in minimally invasive surgical techniques, there is scope to change standard practice to reflect the unique profile of HPV+ OPSCC.

Case report

A 59-year-old man presented to the Head and Neck Cancer Service with a painless, mobile lump on the left side of his neck. He was otherwise asymptomatic and had no relevant past medical history, allergies, or family history of note. On examination, a 2.5cm mobile firm lump was found in level 2 on the left side of the neck. The left palatine tonsil was smoothly enlarged and firm to touch, flexible nasendoscopy was unremarkable. CT neck identified a 16x11x14mm submucosal lesion in the upper half of left palatine tonsil with abnormal adjacent nodes.

Histopathology from the left palatine tonsil showed squamous cell carcinoma staining p16+, suggesting HPV positivity. A left level 2 neck lymph node biopsy showed fibroid tissue infiltrated by islands of small round blue cells with basaloid morphology. This tissue also stained p16+. A PET scan also identified the tonsillar and nodular abnormalities with no sign of distant metastases (figures 1&2). These findings were consistent with metastatic poorly differentiated non-keratinising squamous cell carcinoma with basaloid features of oropharyngeal origin. The final diagnosis was T2N1M0 squamous cell carcinoma of the left palatine tonsil, p16+.

Current UK guidelines state that treatment options for low stage OPSCC include radical radiotherapy or transoral surgery and neck dissection[7]. The patient consented to take part in the PATHOS clinical trial, enabling surgical intervention to take place. PATHOS is a multicentre phase III trial for patients with T1-3 N0-N2b HPV+ OPSCC who have a primary tumour that is trans-orally resectable[8]. Following surgery, patients are divided into three groups, each receiving a different adjuvant therapy. This allocation is based on risk factors for OPSCC recurrence. Patients will either receive no adjuvant treatment (low risk), high or low dose radiotherapy (intermediate risk) or chemoradiotherapy and radiotherapy or radiotherapy alone (high risk). The patient underwent a left tonsillectomy and left neck dissection and is awaiting adjuvant therapy.

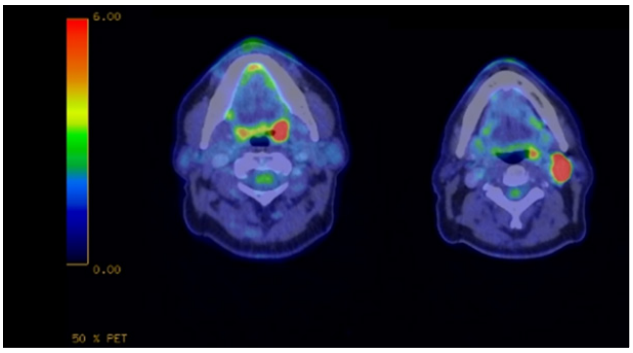

Figure 1: Axial PET scan of the patient's head and neck. Left image shows high FDG uptake in left palatine tonsil. Right image shows high FDG uptake in left level 2 neck lymph nodes.

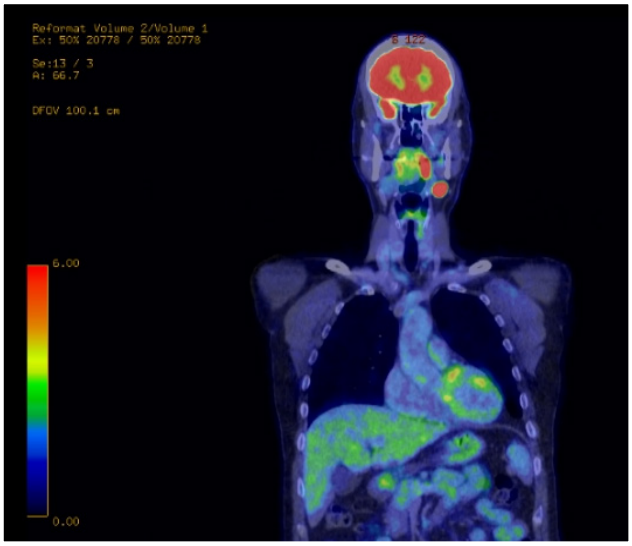

Figure 2: Coronal PET scan of the patient's head, neck, and chest. Scan shows high FDG uptake in left palatine tonsil and adjacent neck nodes with no visible metastases.

New surgical techniques for resectable OPSCC

Over the last 20 years, enormous advances in the surgical treatment of OPSCC have taken place. Driven by renewed interest in the field as a result of increasing HPV positivity and the associated increase in surgically fit patients, new approaches such as TLM and TORS have offered a route away from the functional complications associated with open surgery. The traditional approaches include mandibulotomy, mandibulectomy, and/or pharyngotomy often with neck dissection. Due to the complex and invasive nature of these techniques, patients may experience prolonged hospitalisation, cosmetic deformity and may have to rely on a tracheostomy[2] and/or feeding tube. With the advent of minimally invasive transoral surgery, it is no surprise that TLM and TORS have been increasing in popularity.

Transoral laser microsurgery. TLM is a minimally invasive endoscopic approach with reduced morbidity compared with open surgery. TLM uses a CO_2 laser under the operating microscope and resecting the tumour piece-by-piece. At the beginning of its development, this piecemeal approach to tumour resection was highly controversial as it is generally accepted that tumours should be resected en-bloc[9]. TLM only gained acceptance after a landmark publication by Steiner et al. in 1993 which concluded great efficacy, as local recurrences were only seen in 0.03% of patients and adjusted five-year survival rates were 100%. Although the efficacy of TLM and open surgery are similar, complications such as poor wound healing and laryngocutaenous fistulation are avoided in the former. TLM also allows a more personalised approach to OPSCC removal as a piece-by-piece resection may improve marginal clearance.

Transoral robotic surgery. TORS has also emerged as a non-invasive alternative to open surgery. The use of TORS was first described on a human in 2005 with the removal of a vallecular cyst[11]. Unlike TLM, TORS takes full advantage of the manoeuvrability and optical power of a robotic system to resect tumours en-bloc. Advantages of TORS include 3D visualisation, an improved range of motion and hand tremor filtration[2]. This technique results in similar oncological outcomes to open surgery[12] and radiotherapy[13]; however, it is the functional advantages that TORS confers which makes it favourable for OPSCC resection. A meta-analysis in 2015 demonstrated promising functional outcomes in early studies using TORS as a primary treatment modality[14]. Moreover, TORS with adjuvant therapy has shown to have fewer detrimental effects on

quality of life (QoL) than primary chemoradiation, and this brief TORS-associated decrease in QoL has been shown to be minimal and transient[15].

These minimally invasive surgical techniques offer a way to avoid the long-term toxicity of chemoradiation and the complications associated with open surgery. Given the altered patient demographic in HPV+ OPSCC, the recommendation of these surgical approaches as first-line treatment in HPV+ patients should be considered. Furthermore, given the favourable prognosis and decreased prevalence of co-morbidities in HPV+ patients, the use of TLM and TORS as the primary treatment modality for these patients may allow for the de-escalation of adjuvant therapies. This would confer a major functional advantage as toxicity of chemoradiation can be limited, and so evidence should be scrutinised to assess whether treatment guidelines should be altered to include HPV status as a treatment-determining factor.

HPV: a case for changing treatment guidelines in OPSCC

In 2000, Gillson et al. first showed the aetiological nature of HPV infection in OPSCC[16]. Over the last 20 years, numerous studies have not only confirmed this, but have built a distinct role for this infection in the epidemiology, molecular profile, and clinical characteristics of OPSCC. In terms of treatment, there is currently no difference between recommendations for HPV+ and HPV- OPSCC. UK guidelines state that T1-T2 N0 OPSCC should be treated with radical radiotherapy or transoral surgery and neck dissection (± adjuvant chemoradiotherapy). Guidelines also state that 'Altering the modalities of treatment according to HPV status is currently controversial and should be undertaken only in clinical trials'[7]. However, given the recent rise in the incidence of HPV+ tumours and new evidence for key differences between HPV+ and HPV- OPSCC, should treatment guidelines should be changed to reflect these?

Important considerations include the demographics of patients diagnosed with OPSCC. HPV-positive patients are younger (median age of 54 years) and have less exposure to alcohol and tobacco[3]. Moreover, biological variability between HPV+ and HPV- oropharyngeal cancers can be shown on a gross level. In a study by Cantrell et al., HPV- OPSCCs were found to demonstrate ill-defined borders and were more likely to invade adjacent muscle tissue[17]. HPV+ OPSCC is also more likely to present at an early clinical stage (T1-T2) and is associated with a lower risk of metastatic disease[18]. OPSCC HPV tumour status has also been shown to be a strong prognostic factor for survival. A retrospective analysis performed by Ang et al. demonstrated that the overall 3-year overall survival rates were 82.4% vs. 57.1% for patients with HPV+ and HPV- OPSCC, respectively[19]. From this, it is clear that the HPV status of OPSCC has a profound impact on the pathophysiology of the disease. However, substantial clinical evidence is needed to drive a change in treatment guidelines. Several clinical trials are currently taking place to assess whether TLM/TORS may be used to achieve favourable functional and oncological results.

Clinical trials investigating the transoral surgical management of HPV+ OPSCC

There has been a surge in trials assessing the use of TLM and TORS in HPV+ OPSCC. These aim to minimise functional morbidities whilst maintaining oncological outcomes[20]. The ADEPT study (NCT01687413) is a phase III trial assessing whether it is possible to omit postoperative chemotherapy in HPV+ OPSCC patients who have undergone transoral surgery. ECOG is a phase II RCT of transoral resection followed by low/standard dose radiotherapy in resectable locally advanced HPV+ OPSCC (NCT01898494). The main aims of this are to determine whether similar oncological and functional outcomes can be achieved with de-escalated adjuvant therapy. Furthermore, the PATHOS trial (NCT02215265), in which this patient is enrolled, is a phase II/III randomised controlled trial in which patients with T1-3 N0-N2b HPV+ OPSCC undergo transoral surgery followed by different regimes of adjuvant therapy. PATHOS aims to study the safety, efficacy, and functional outcomes of minimally invasive transoral surgery followed by de-escalated adjuvant therapies. From the studies above, it is clear that new techniques such as TLM and TORS are being investigated for their functional outcomes and efficacy in the treatment of OPSCC. Although theoretical and preliminary evidence shows improved functional outcomes, more evidence is needed to assess whether treatment guidelines should be changed with respect to HPV status.

Conclusion

The profile of OPSCC is changing rapidly with the increasing incidence of HPV. Human papillomavirus affects both the patient demographic and oncological characteristics of OPSCC, leading to more surgically viable patients. With recent technological advancements in transoral surgery, approaches such as TLM and TORS are more appropriate to treat HPV+ OPSCC. These avoid complications associated with open surgery and the long-term toxicity associated with chemoradiation. The distinct biological profile of HPV+ OPSCC has also led to discussion about whether HPV status should be added to treatment guidelines and whether treatment can be de-escalated to reduce functional morbidities associated with current treatment. Several important clinical trials are underway to determine whether OPSCC treatment should be altered due to the rising prevalence of HPV+ OPSCC; these will define treatment guidelines for the future.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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