

From Oral Sex to Robotic Surgery

The paradigm shift in oropharyngeal cancer

by Dr Jeeve Kanagalingam

Paradigm shifts are few and far between in the field of cancer research and treatment. One is presently occurring in the field of oropharyngeal cancer which includes the tonsils and tongue base **[Figure 1]**. Previously a disease in older men who smoke and consume alcohol, there is a rising incidence amongst the young who neither smoke nor drink. In this group, the human papillomavirus (HPV) that is known to cause cancers of the uterine cervix, vulva, vagina, anus and penis is the causative factor too.¹ The transmission of this virus is by oral sex – with rising rates of prevalence amongst those with multiple oral sex partners.

These HPV-positive tumours are exquisitely sensitive to radiotherapy and portend a better prognosis. The five-year overall survival rates in these tumours surpass 80% compared to 40% for HPV-negative stage III/IV tumours. The paradigm shift not only changes the way we treat these tumours but also raises important considerations in prevention, screening and counselling.

The rising incidence of HPV-positive Oropharyngeal Cancer

In the United States, there has been a large rise in oropharyngeal cancer in recent decades. US data suggest that the annual rate of increase between 1973 and 2004 has been 0.8%.² A third of head and neck cancers in the US today arise from this sub-site. Similarly, data from Singapore suggests that between 1993 and 2002 there has been a 57% rise in incidence of oropharyngeal cancer.³

Sixty percent of oropharyngeal cancer in the United States is associated with HPV16 infection. In Singapore, unpublished data from the National University Hospital suggest that 41% of oropharyngeal cancer is HPV-related. It is likely that the 'epidemic' of HPV-positive oropharyngeal cancer has reached the shores of Singapore, and will soon make up a significant portion of head and neck cancers, as nasopharyngeal cancer declines in incidence.



Figure 1. Left tonsillar tumour extending to involve the soft palate – this tumour proved positive on immunohistochemical stains for HPV.



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Features of HPV-positive oropharyngeal cancer

In the US, HPV-positive oropharyngeal tumours appear to affect middle-aged white men from a higher socio-economic status who consume less tobacco and alcohol. These men tend to have multiple oral sex partners. It is postulated that it is easier to contract HPV from performing oral sex on a woman than on a man, hence the higher rates of these tumours amongst men. HPV-positive oropharyngeal tumours tend to be smaller at diagnosis than HPV-negative tumours but appear to have more advanced nodal disease in the neck.

Several multi-institutional trials of chemoradiation for oropharyngeal cancers (RTOG0129, ECOG2399, TROG02.02, TAX324 and DAHANCA) have shown a superior survival benefit among HPV-positive tumours [Table 1]. The landmark RTOG0129 study authored by the late Kie Kian Ang showed risk stratified cases based on HPV status of the tumour and smoking status of the patient.⁴ This study elegantly demonstrates that the survival benefit conferred by HPV-positive status is greatly diminished by smoking behaviour [Figure 2].

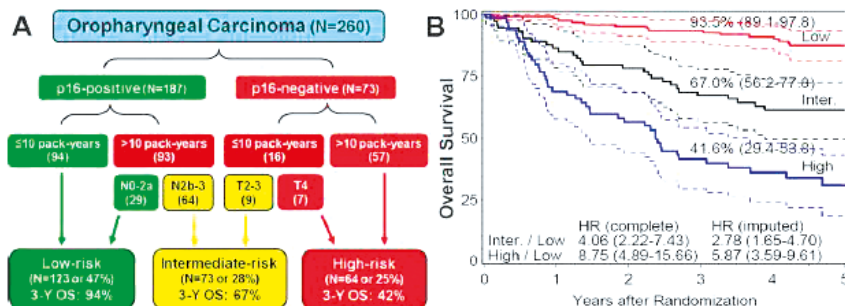


Figure 2. Results of the RTOG0129 study showing the effects of HPV and smoking on the outcome of oropharyngeal cancer (from Ang KK, Harris J, Wheeler R et al)

Table 1. Favourable outcome of HPV-positive vs HPV-negative oropharyngeal tumours in multicentre trials

Study	N	Assay	Endpoint	Hazard Ratio	p-value
ECOG2399	96	ISH, p16	Tumour progression	0.27	0.01
RTOG0129	323	ISH, p16	Overall survival	0.42	<0.001
			Progression-free survival	0.49	<0.001
TROG02.02	185	P16	Overall survival	0.36	0.004
			Failure-free survival	0.39	0.003
TAX324	111	PCR (E6, E7)	Overall survival	0.20	<0.0001
DAHANCA	794	P16	Overall survival	0.62	<0.001
			Disease-specific survival	<0.001	0.001

HPV in the Oncogenesis of Oropharyngeal Cancer

There are various subtypes of the human papillomavirus. Subtypes 16 and 18 have been associated with cervical cancer. In oropharyngeal cancer, HPV16 predominates – accounting for almost 90% of HPV-positive tumours. The odds ratio for oropharyngeal cancer amongst subjects who are seropositive for HPV16 is more than 14.⁵ The virus encodes for two oncogenic proteins – E6 and E7 – which inactivate tumour protein 53 (p53) and retinoblastoma tumour suppressor gene products, respectively.^{6,7} This disrupts the cell cycle regulatory pathways and promotes oncogenesis.

Trans-oral Robotic Surgery (TORS) and De-escalation of Treatment

Prior to the advent of chemotherapy and organ-preservation strategies in head and neck cancer treatment, oropharyngeal cancer was treated with either surgery followed by radiotherapy, or radiotherapy followed by neck dissection for residual neck disease. The five-year survival outcomes were modest at 47% for surgery followed by radiotherapy, and 43% for radiotherapy with or without neck dissection.⁸ Surgery was morbid, involving splitting the jaw (mandibulotomy) to excise the tumour [Figure 3], and this led to the use of concurrent chemoradiation in definitive treatment of this cancer.

In 2005, Neil Hockstein – then an Otolaryngology resident at the University of Pittsburgh – modified a surgical robot for use in the upper aerodigestive tract. This gave rise to Trans-oral Robotic Surgery (TORS). In

TORS, the surgeon sits at a console, controlling the robot which has surgical 'arms' that are small and dextrous enough to access the tumour **[Figure 4]**.

Greg Weinstein and Bert O'Malley of the same institution later published the first series of tumours treated with TORS.⁹ Since then, there has been an exponential rise in the number of tumours treated with TORS first with or without adjuvant radiotherapy. HPV-positive oropharyngeal tumours, which have small volume primary disease but advanced nodal disease in the neck, are ideally suited to this treatment strategy.

Early data from the Mayo Clinic shows that it is possible to resect even stage IV tumours with TORS and maintain clear margins of resection. Their data showed an impressive two-year disease-specific survival

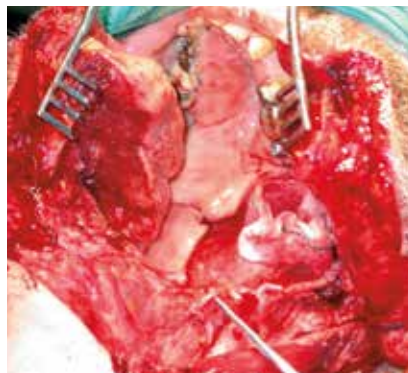


Figure 3. The classical COMMANDO operation – in which the jaw is split to access the oropharynx



Figure 4. Trans-oral Robotic Surgery (TORS): The surgeon sits at a console and has high-definition 3-D vision of the operative field. The robotic arms enter the oropharynx and enable precise dissection of the tumour.

of 95.1%, and a two-year recurrence-free survival of 92.4%. Functional outcome was excellent, with 97% of patients able to eat within three weeks. The permanent gastrostomy tube rate was 4.5%, and the long-term tracheostomy rate was just 1.5%.¹⁰

The recognition that HPV-related oropharyngeal tumours have a more favourable outcome has led many investigators to study less intensive treatment aimed at reducing morbidities without compromising on tumour control and survival outcome. De-escalation of treatment – by reducing the total dose of radiotherapy received and omitting or using less toxic chemotherapy – is now more attractive. Trials – such as the ECOG E1308 and the De-ESCALaTe HPV – are in progress and preliminary results are promising.

Prevention, Screening and Counselling

With the availability of vaccination against HPV, we now have the first effective preventative strategy – besides smoking cessation – against a head and neck cancer. Both leading vaccines – Cervarix and Gardasil – protect against HPV16, which is the main strain responsible for oropharyngeal cancer. Given that HPV-positive oropharyngeal cancer is more common in

men, the case for vaccinating boys in addition to girls is stronger.

For those already exposed to HPV, there is now hope of a simple screening test for HPV. A recent study showed that HPV E6 antibodies were present in 34.8% of pre-diagnostic samples of cancer cases and only 0.6% of controls. The time from seroconversion to cancer diagnosis was up to 10 years. This may help identify high-risk patients who require closer surveillance.

Finally, the implication of diagnosing an HPV-positive oropharyngeal tumour raises important considerations in counselling patients and their loved ones. The sympathy that a spouse has for a patient may rapidly give way to anger when the significance of an HPV-related tumour is made known to them. The recent separation of Michael Douglas and Catherine Zeta-Jones after his revelation of the HPV status of his throat cancer serves as a poignant illustration of this problem. **MGC**

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