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CURRENT TREATMENT AND MANAGEMENT OF OROPHARYNGEAL CANCER: A REVIEW

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ABSTRACT

In both the developing and developed worlds, oropharyngeal squamous cell carcinoma (OPSCC) is becoming more common. Treatment paradigms for OPSCC have shifted dramatically in recent years. This is due to a number of factors, including the identification and understanding of a new viral aetiology (the human papillomavirus [HPV]), changes in practise patterns due to breakthroughs in radiation, and finally an organ preservation strategy with greater chemotherapy use. The focus of the review is on the progression of oropharyngeal squamous cell carcinoma, as well as treatment trends and outcomes in oropharyngeal cancer.

KEYWORDS: Oropharyngeal squamous cell carcinoma, Treatment, Management and Review.

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) refers to squamous cancers that develop in the posterior third of the tongue, tonsils, soft palate, and posterior pharyngeal wall.[1] Within these subsites of the oropharynx, the tonsil and tongue base are the most common sites to be affected by carcinoma. These sites differ from the other subsites because they have a high density of lymphoid cells and show a strong association with human papillomavirus (HPV)-related squamous carcinoma. The strong predilection of HPV for the oropharynx is due to the microanatomy of the reticulated epithelium (epithelium with an immune system component) of the base of the tongue and tonsils.[2] HPV infects the reticulated epithelium lining the deep tonsillar crypts. The deep crypts of tonsils are immune-privileged sites, which means they can tolerate the introduction of antigens without eliciting an inflammatory

immune response. This results in inhibition of the effector function of the HPV-specific T cells and thereby facilitates immune evasion at the time of initial HPV infection.[3]

The evolution of oropharyngeal squamous cell carcinoma

Tobacco era

Traditionally, oropharyngeal carcinoma was closely related to tobacco and alcohol exposure. The incidence of carcinoma in the oropharynx was similar to that in the other sites of the upper aero-digestive tract that all shared common exposure to the carcinogens in tobacco. There was also a high incidence of comorbidity in these patients from associated tobacco exposure conditions. Treatment was typically with surgery, as most tumors were locally advanced at presentation. Open approaches, such as mandibulotomy, were used to access the oropharynx. Longterm support of airway and feeding was often required in the form of a gastrostomy feeding tube and a tracheostomy. Radiotherapy was used post-operatively to optimize loco-regional control. With developments in the delivery of radiation and the recognition that primary non-surgical management was feasible, a move away from traditional open resection was seen. Two multi-center randomized controlled trials in 2004 also showed a survival advantage with the addition of post- operative chemoradiotherapy in high-risk patients.[4]

Radiationbased approaches were adopted more commonly with surgery reserved for salvage. A report of the outcomes and complications comparing surgical and radiotherapy-based approaches in 2002 showed that while both approaches had similar survival and local control rates, surgery was associated with an increased rate of complications.[5]

Organ preservation era

Landmark trials fueled the enthusiasm for organ preservation approaches in head and neck cancers and built upon increasing radiation treatment experience and expertise. In 1994, the Veterans Affair study reported outcomes for locally advanced laryngeal carcinoma treated with induction chemotherapy followed by radiotherapy (in responders) compared with total laryngectomy. The results of this study confirmed that a non-surgical organ preservation approach could be adopted, which achieved similar oncological outcomes but avoided laryngectomy in over 60% of cases.

A further study in locally advanced laryngeal carcinoma by Forastiere et al. showed a survival benefit in the use of concomitant chemoradiotherapy (chemotherapy administered

during radiation) over induction chemotherapy or radiation alone. These results were extrapolated to other head and neck sites and provided the initial support for organ preservation strategies. The first major OPSCC-specific trial was authored by the GORTEC group. They randomized 266 patients with OPSCC to concomitant chemoradiotherapy or radiotherapy alone. An overall survival at 3 years was reported as 51% in the chemoradiotherapy group versus 31% for the radiotherapyalone group. At 5 years, a 6.6% overall survival benefit with the addition of chemotherapy was reported. This has subsequently become a standard therapy for loco-regional advanced OPSCC and was supported by a robust meta-analysis.[6]

Improvements in radiation

Further interest in radiation treatments for OPSCC was stimulated by advancing technologies in the delivery of radiotherapy. Intensity-modulated radiotherapy treatment (IMRT) was introduced in the early 2000s. This was a new radiotherapy technique aimed at reducing the comorbidity of treatment by allowing the oncologist to manipulate radiation dose in a way that would increase accuracy and reduce the dose to bystander structures. Specific potential advantages of this targeted method of delivering radiation include avoidance of high-dose exposure to the parotid glands to minimize xerostomia and to the pharyngeal constrictors in an attempt to minimize swallowing dysfunction. Human papillomavirus era The next major development was the discovery of a viral etiological agent in the carcinogenesis of OPSCC. An association of HPV with carcinomas of the tonsil and base of the tongue emerged in the early 1990s, with the identification of HPV DNA in tumor cell nuclei and viral oncogene transcription in tonsillar carcinomas.[7]

The proportion of OPSCC with detectable HPV DNA on testing approached 50% in a number of series, but the rate does vary by country. A UK series has shown up to 70% of oropharyngeal tumors are HPV related. The HPV16 subtype is the most common and is found in 90% of tumors. The other high-risk subtypes 31, 33, and 18 have also been identified. In an East Denmark study between 2000 and 2010, Garnæs et al. found 58% of tonsillar OPSCC were HPV-related tumors and 51% in the base of the tongue were also HPV related. However, high-risk HPV DNA showing evidence of transcription is infrequently seen at other sites in the head and neck and at the subsites of the soft palate and posterior pharynx. A multicenter cross- sectional retrospective study in the UK, however, has confirmed an

increase in OPSCC cases but also showed that the percentage of tumors that were HPV related remained static.[8]

This difference in anatomical location has allowed for the investigation of population-level data. An analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2004 with patients deemed likely to be HPV positive based on if the tumor's location was in the tonsil or the base of the tongue showed patients were younger (61.0 versus 63.8 years, $p<0.001$)23. A series of 193 patients, using DNA PCR to test for HPV, showed that HPV-positive tumors were more likely to affect patients younger than 55 years old. Age was recognized as an important distinction between HPV-positive and -negative tumors in a study from Sweden. Patients with HPV-related cancers were younger (mean age of 59 years [range 42–78] versus 66 years [range 45–89]).[9]

Additionally, USA SEER data indicated that men have a higher incidence of OPSCC than do women and that blacks are more commonly affected. However, when likely HPV-positive tumors are examined, they were seen to have a higher incidence in white men and an increasing incidence in men in all other races. There was also a correlation between the educated middle class and HPV-positive cancers.

Other differences between HPV-positive and -negative tumors have also been seen. Tobacco has been identified as a head and neck cancer risk factor; it also acts synergistically with alcohol. A 25,500-patient multicenter study found that tobacco is a major risk factor for head and neck and oropharynx carcinoma. Patients with HPV-positive tumors have been shown to be non-smokers more often, and the overall tobacco use is lower compared to that in HPV-negative patients. However, smoking is still a risk factor but has less of an impact in HPV-related cancers. Patients with HPV-positive tumors have about 30% non-smokers in their group compared with less than 5% in the HPV-negative groups. This relationship has been seen in a number of studies.[10]

Treatment trends and outcomes

In a study using the National Cancer Database (NCDB), a North American governmental database of cancers and treatments, the trends in the treatment modalities used in OPSCC were examined. In an analysis of 43,983 patients between 1998 and 2009, the number of patients receiving chemoradiation increased from 22% of all patients in 1998 to 61% in 2009. This has been accompanied by a concurrent decline in the percentage of patients receiving

surgery, from 41% in 1998 to 31% in 2009. This coincides with the increasing incidence of OPSCC and increased HPV-related disease.[11]

In recent studies using modern IMRT techniques, outcomes of chemoradiation for OPSCC have been excellent. In a European study37 analyzing the survival and toxicity outcomes with primary IMRT, 186 patients received IMRT with 90% of loco-regionally advanced disease receiving concurrent chemotherapy or cetuximab. The estimated 3-year overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) rates were 77.2% (70.5–83.9), 72.3% (65.4–79.2), and 80.2% (74.1–86.3), respectively. Estimated 3-year OS, DFS, and DSS rates for HPV-positive patients were 90.9% (85.2–96.6), 87.9% (81.4–94.4), and 91.8% (86.3–97.3), respectively.

Despite the excellent oncological results achieved with this approach, the changing demographic of patients with OPSCC and the improvement in survival means new challenges are being seen. The complications and sequelae of treatment are now more pertinent because patients are younger, more likely to be cured, and more likely to live longer.

Bird et al.[12] reported that three (1.6%) patients died during or within 30 days of radiation completion, 74 (40%) were admitted at least once during their radiotherapy, and 76% needed a feeding tube either as a supplement to their oral intake or to meet their complete nutritional requirements. However, long-term toxicities are likely to be more important in understanding which treatment is best for patients, as all treatment approaches are associated with acute toxicity.

Minimally invasive surgery era

Our understanding of OPSCC etiology and its relationship with HPV infection has evolved at a time when non-surgical organ preservation approaches in head and neck oncology have replaced more traditional open surgeries with post-operative radiotherapy. However, over a similar time frame, significant progress has been made in surgical technology. Advances in optics and instrumentation have made a number of options available for the removal of head and neck cancers via a trans-oral endoscopic route.

In 2005, Melder and McLeod reported its first use in head and neck surgery when they performed a resection of a vallecular cyst. In 2006, Weinstein et al. at the University of Pennsylvania reported the robot's first application to head and neck malignancy; their group

conducted most of its early research and coined the term TORS. Subsequently, in 2009, the FDA approved its use in the head and neck, and TORS is now utilized worldwide.

Trans-oral surgery has emerged as an approach that offers an alternative to open surgery and primary non-surgical treatments and is being used in the staging/diagnosis of unknown primary patients.[13]

The advantages of TORS are the ability to operate without line-of-sight restrictions that limit other trans-oral endoscopic or microscopic approaches. The approach offers a consistent approach in which the pharyngeal muscle constrictors are removed to provide a deep margin. It allows tumors that would normally demand a pharyngotomy or mandibulotomy to be resected. Additionally, it involves instruments with six degrees of freedom, motion scaling, instrument stabilization, and tremor reduction.[14]

Trans-oral laser microsurgery (TLM) and TORS have demonstrated excellent oncological results for many indications and subsites, mostly in single institutional studies and oropharyngeal disease. TORS has also shown promising functional outcomes with appropriate adjuvant therapy. A multiinstitutional study of TORS has recently reported a 3-year survival rate of 92.5% and a 3-year recurrence rate of 88.8%.[15]

Immunotherapy era

The most recent development in the treatment of head and neck cancer is immunotherapy. Significant progress has been made in the application of immune checkpoint inhibitors such as nivolumab, pembrolizumab, durvalumab, atezolizumab, and avelumab. The checkpoint inhibitors pembrolizumab and nivolumab are FDA approved in the recurrent and metastatic setting and have an established paradigm for use. The majority of current studies are assessing drugs in the end-stage setting and also using a combination of treatments.[16]

However, there are currently 16 trials exploring the use of these drugs in the primary setting with curative intent. A majority of these drugs act on the PD1 (programmed cell death protein)/PDL1 axis. This is applicable to head and neck and OPSCC because the oropharynx is known to be an immuneprivileged site. The reticulated epithelium is known to express the immune checkpoint ligand PDL1, and the resulting reduction in cytotoxic T cell response has been linked to persistent HPV infection at these sites.[17]

CURRENT TREATMENTS AND TRIALS

Current treatment options

Despite major differences in the risk factors, demographics, clinical behavior, response to treatment, and molecular patterns of HPV-positive compared to HPV-negative tumors, the recommended treatment options are still the same, unless the patient is on a trial. Treatment is decided using the Tumor, Node, Metastasis (TNM) stage, the patient's preferences, the patient's co- morbidities, and the physician's experience. For loco-regionally advanced oropharyngeal cancer, dual modality treatment with either trans-oral surgery and post-operative radiotherapy with or without post-operative chemotherapy or concurrent chemoradiotherapy is usually offered. In cancers of the tonsil and base of the tongue, chemoradiotherapy is used more frequently. Early stage disease can be treated with single modality treatment, such as surgery or radiotherapy alone.[18]

The long-term toxicities following chemoradiotherapy have been questioned and have provided impetus and enthusiasm for trans-oral resection as a primary treatment for these tumors. There are no randomized trials comparing trans-oral approaches versus IMRT, and the majority of the literature is limited to uncontrolled reports. Comparable oncologic outcomes with TORS compared to IMRT have been reported in these studies and functional outcomes may be superior. However, current follow-up is relatively short, and the TORS studies include patients with earlier-stage OPSCC on average compared to comparable IMRT studies.

Current trials in OPSCC

The use of surgery in HPV-positive oropharyngeal cancer and the application of minimally invasive techniques to avoid or reduce required doses of adjuvant treatment have become important areas of study. Trans-oral laser surgery (TLS) was first popularized by Steiner in Germany. There has been increasing experience with TLS, but its use for oropharyngeal tumors has been limited to a few high-volume centers in the USA58 and European units in the UK, France, and Germany.[19]

De-escalation based on surgical resection and the neck stage is being assessed in HPV-positive tumors In the Sinai Robotic Surgery Trial (NCT02072148). Another study, conducted at the University of Pennsylvania, is employing robotic surgery to de-escalate adjuvant treatment. Reduced treatment to the primary tumor bed in fully resected tumors (NCT02225496) is being investigated.

The ADEPT trial (Post-Operative Adjuvant Therapy De-intensification Trial for HPV-related, p16+ Oropharynx Cancer) examined patients with fully excised HPV-positive tumors and randomized patients to either radiotherapy or radiotherapy plus cisplatin (NCT01687413). It is now closed to accrual. The use of post-operative docetaxel with hyper-fractioned IMRT is being investigated in another trial following minimally invasive surgery (NCT01932697).

In the Canadian ORATOR trial, a phase II randomized trial, patients with early stage OPSCC were randomized to receive radiotherapy or trans-oral robotic surgery with neck dissection (NCT01590355). In this "best of" randomized study, patient-reported swallowing function over the first year will be investigated following allocation to either IMRT or TORS in patients with early stage OPSCC (NCT02984410).

There are a number of other trials that are using modification of the standard radiotherapy or chemotherapy techniques. In HPVpositive oropharyngeal tumors, cisplatin alternatives are being trialed, as they are thought to have less toxicity. With concurrent radiation, epidermal growth factor receptor (EGFR) therapies are being investigated. Cetuximab is the most common agent. It is a monoclonal antibody that targets the EGFR extracellular ligand-binding domain on the cell surface.

The Radiation Therapy Oncology Group (RTOG) are conducting a randomized trial of cisplatin versus cetuximab with radiation (NCT01302834). De-ESCALaTE (Determination of Cetuximab Versus Cisplatin Early and Late Toxicity Events) is a UK trial comparing either cisplatin or cetuximab with radiation and using toxicity as a primary outcome (NCT01874171). Also, the Australian Trans-Tasman Radiation Oncology Group (TROG) have a trial comparing cetuximab to cisplatin with radiotherapy (NCT01855451). An additional study is investigating cetuximab with pre- and post-treatment biopsies, which will then be compared to a historical series of cisplatin-treated patients (NCT01663259).

Chemotherapy with high- or low-dose radiation or just radiation alone is being investigated in stage III or IV HPV-related OPSCC (NCT02258659). Paclitaxel and carboplatin used as an induction therapy with concomitant paclitaxel in tumors of HPV-positive patients is another regimen under investigation (NCT02048020).

In HPV-positive patients, reducing the radiation dose is another approach. Reduction of the dose of IMRT to 54–60 Gy while simultaneously administering weekly intravenous cisplatin will precede surgical resection of any clinically apparent residual tumor or neck disease (NCT01530997). A randomized trial of HPV-positive oropharynx tumors using a reduced dose of IMRT treatment with randomization to radiotherapy alone or concomitant cisplatin presents an additional approach (NCT02254278).

Treatment de-intensification is being investigated in another study alongside cisplatin chemotherapy with a reduced radiation dose, with the experimental arm's dose decreasing from 70 Gy to 63 Gy (NCT01088802). There are other new agents and immune therapies currently being trialed. Ribavirin is being evaluated as part of a phase I trial. It is a drug that is used in the treatment of hepatitis C, and it is being used with afatinib (a tyrosine kinase inhibitor) as an induction chemotherapy agent with weekly carboplatin/ paclitaxel dose (NCT01721525).

In contrast to efforts to de-escalate treatment of HPV-positive low-risk tumors, HPV-negative tumors and some HPV-positive tumors in patients with a smoking and alcohol history are deemed high risk. In these patients, there may be benefit in escalating treatment to improve outcomes. In the COMPARE trial (UKCRN Study ID: 18621), additional treatments in conjunction with standard chemoradiotherapy are being investigated compared to standard chemoradiotherapy. Patients are randomized to either the standard or receive surgery followed by chemoradiotherapy, more chemotherapy as induction (docetaxel, cisplatin, and 5-fluorouracil), a higher dose of radiotherapy as part of their chemoradiotherapy, or durvalumab with chemoradiotherapy.

CHANGES IN TESTING AND STAGING

Testing for human papillomavirus

There has been controversy regarding the different techniques and biomarkers used to determine whether a tumor is related to HPV infection. Sustained and persistent high-risk HPV E6/E7 viral oncogene expression is essential for a HPV-driven malignant tumor. The detection of HPV E6/E7 mRNA transcripts correlates with cellular genotoxic damage and gene expression changes that are the hallmarks of cancer. However, the detection of mRNA in the clinical setting is difficult and expensive61. Another approach is using p16 as a surrogate for HPV infection and could utilize the cheaper and more available immunohistochemistry stains. However, when a number of these different assays were tested,

only the RT-PCR assay for HPV16 E6*I mRNA developed specifically for formalin-fixed paraffin- embedded (FFPE) material was able to accurately classify samples.[20]

Using the different biomarkers for prediction of outcome, the doubly positive p16/HPV DNA test had the best predictive ability, with p16-positive/HPV-negative tumors having a prognosis closer to more typical non-HPV-related tumors. Therefore, it has been proposed that the combination of p16 immunohistochemistry and the detection of HPV DNA by PCR is required63. Other testing methods for HPV infection involve the use of saliva samples from swish and spit specimens. This may provide a potential screening test for OPSCC or may replace the need for formal biopsy.[21]

OPSCC has been divided into p16-positive, high-risk HPV- associated tumors and p16-negative tumors. In the T staging category, the Tis and T4b stages have been removed from HPV-related tumors. There has been the introduction of separate clinical and pathological N staging systems. The clinical N staging has been simplified, with the N1 stage now including all patients with ipsilateral nodes less than 6 cm. This will downstage patients who previously had T2b neck disease in the seventh edition. N2 disease includes patients with contralateral or bilateral disease, and N3 is for patients with a neck mass of more than 6 cm. In the pathological staging system, N1 disease is fewer than four positive nodes, N2 is more than four positive nodes, and N3 has been removed.

EVOLUTION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA MANAGEMENT (THE SWINGING OF THE PENDULUM)

Before the publication of the Veterans Affairs (VA) study (1991), most institutions treated HNSCC with surgery with (or without) adjuvant therapy. Classic surgical approaches to the oropharynx consist of en bloc resection of the primary tumor. The three primary open techniques used for OPC include lip-split mandibulotomy (mandibular swing), suprahyoid (transhyoid) pharyngotomy, and pull-through techniques using a visor incision.[22]

Surgical morbidity following these approaches can be significant; complications reportedly range from 10–60%, and include speech and swallowing difficulties, malocclusion, temporomandibular joint pain, cosmetic deformity, fistula formation, and severe dysphagia in 7–18% of cases.[23]

Chemoradiotherapy (CRT) itself is not risk free. Mucositis, xerostomia, osteoradionecrosis, pharyngeal and esophageal scarring/stenosis, and constrictor muscles fibrosis leading to speech and swallowing disorders, renal failure, sepsis, and development of second primary malignancies are all complications of CRT.[24] Radiation therapy (RT) used as single modality treatment for early OPSCC has shown excellent results. Five-year local control rates using primary radiotherapy range from 83–96% for T1 and 54–92% for T2 tumors.

Recent advances in RT have been made, particularly intensity-modulated radiotherapy (IMRT), which has clear theoretical advantages over conventional radiation in multiple tumor types. Excellent target coverage and normal tissue sparing are the two main features of IMRT. The shape, location, and often the extent of OPSCC make them all suited to IMRT.

The rising incidence of HPV-associated OPSCC over the last 2 decades has driven another movement for changes in management strategies. Renewed interest in finding an operative approach for OPSCC management led to the introduction of transoral surgery, including transoral laser microsurgery and transoral robotic surgery (TORS).[25]

TORS emerged as a technique capable of providing several benefits over existing treatments and open surgery for head and neck cancer, including reductions in operative times, blood loss, time in intensive care, and overall duration of hospitalization. Moreover, the histopathological information gained improves staging and guides subsequent decision making, providing useful information for tailoring therapy, or personalizing treatment commensurable with the disease: more aggressive treatment for high-risk and less aggressive for low-risk patients.[27]

Additionally, most patients have their surgical wounds left for secondary healing which usually results in sensitive mucosal coverage. Structural considerations for reconstruction include maintaining separation between neck and pharynx and coverage of the internal carotid artery (ICA) to prevent catastrophic hemorrhage.[28]

The purpose of this article is to review the role of TORS in the management of OPSCC, its indications, techniques, outcomes, and costs. New information on comparisons between TORS, conventional surgical techniques, and CRT is also highlighted.

TRANSORAL ROBOTIC SURGERY FOR SALVAGE OF RECURRENT OROPHARYNGEAL CANCERS TORS

Seems to offer a reasonable alternative surgical approach to recurrent tumors of the oropharynx with acceptable oncologic outcomes and better functional results compared with open surgical approaches. A multicenter comparison of recurrent oropharyngeal disease treated with TORS (64 patients) and open resection (64 patients) was published in 2013. In this series, TORS resections had a significantly decreased incidence of positive margins (6 versus 19; P ¼ 0.007) and a significantly higher RFS than the open approach group (74 and 43%; P ¼ 0.01). Furthermore, patients treated with TORS had a lower incidence of tracheostomy (14 versus 50; P < 0.001) and feeding tube use (23 versus 48; P < 0.001), and shorter overall operative time and hospital stay (3.8 versus 8.0; P < 0.001).[29]

TRANSORAL ROBOTIC SURGERY FOR THE MANAGEMENT OF UNKNOWN PRIMARY HEAD AND NECK CANCER

Identification of the primary site in head and neck cancer is crucial, allowing for a more focused radiation field, reducing morbidity related to a broader field of radiation, and offering an opportunity for definitive surgical management based on the location. Previous studies have reported that identification of occult primary tumors results in increased survival rates from 58 to 100% versus 16 to 50% for those not localized. Several recent studies have demonstrated improved primary site identification rates using TORS to remove all lingual tonsil tissue. A multicenter study with 47 patients with unknown primary head and neck cancer using TORS was able to find the primary tumor in 72%. An observational cohort study of 65 p16þ unknown primary patients treated with TORS and neck dissection (2001–2012) was able to detect the primary site in 89% (58/65) of cases. Interestingly, the 5-year DSS and OS was 98 and 97%, respectively, for the detected and 100% for the undetected group. Most importantly, of the 47 patients receiving adjuvant therapy, radiotherapy spared the pharynx in 36. These results favor TORS as a useful approach for identifying and treating the primary site in patients with unknown primary HNSCC.[30]

QUALITY OF LIFE AND TRANSORAL ROBOTIC SURGERY

Quality of life (QOL) measurements have become a vital and necessary part of health outcome appraisal. For populations with chronic disease, QOL measurement provides a meaningful way to determine the impact of health care when cure is impossible. Functional

outcomes have recently played an increasingly important role in our treatment choices, but studying this aspect of cancer care remains unsystematic.

The use of TORS alone had minimal, temporary effects on speech and TORS and radiation had significantly fewer detrimental effects on QOL than the utilization of combined CRT. These results substantiate the benefit of TORS as a viable treatment that reduces the overall morbidity associated with current classic CRT treatment alone for head and neck cancers.[31]

CONCLUSION

OPSCC is a field that is still developing. In the majority of cases, surgery and radiation therapy were the only alternatives for treatment for many years. While this is true, a number of fresh and intriguing choices are emerging. Advances in radiation techniques, such as IMRT, allow for more precise dosage administration to the tumour while sparing surrounding structures, resulting in fewer side effects. As our understanding of the biology of HPV-related disease has improved, efforts have been made to de-intensify treatment regimens in low-risk patients in order to lessen the morbidity of therapy. State-of-the-art technology, such as new robotic and laser systems, has been incorporated into surgical techniques. These advancements have the potential to lessen the long-term morbidity associated with chemoradiation, as well as aid in the intensification of treatment for HPV-negative individuals at the highest risk.

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