New Therapies in Head and Neck Cancer

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Abstract

Squamous cell carcinoma of the head and neck (HNSCC) is the most frequent malignancy of the head and neck region. The most prevalent risk factors include smoking, binge drinking, and infection with the human papillomavirus (HPV). While global smoking rates are declining, HPV-related HNSCC rates are rising in the United States and Western Europe, prompting a shift in our knowledge of the disease's pathogenesis, therapy, and prognosis. The prognosis for non-metastatic HNSCC is still extremely good, and it’s getting better. Radiation technology and techniques have advanced, as have organ preservation surgery options and interdisciplinary therapy choices. However, there is still a gap in the management of metastatic disease. Although the progress of immune checkpoint inhibitors has resulted in much better results, only a tiny percentage of patients benefit. The majority of individuals with recurrent and/or metastatic HNSCC continue to have a dismal prognosis. This has prompted extensive research into new biomarkers and biomarker-based therapeutics. Adaptive cellular therapy and therapeutic vaccinations are two new treatment alternatives on the horizon. In this review, we highlight the most recent developments in the field of HNSCC as well as the research's future directions.

Keywords: Head and neck squamous cell carcinoma; recent advances; chemotherapy; radiotherapy; surgical technique

BACKGROUND

Squamous cell carcinoma is the most common histology (85 percent) in head and neck cancers, which arise in the oral cavity, pharynx, and larynx. Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent cancer in the world, with an annual incidence of over 600,000 cases and 350,000 deaths. About two-thirds of newly diagnosed patients have advanced-stage illness, mainly with regional lymph node involvement, and 10% have distant metastases. Tobacco use and alcohol intake are two of the most prominent predisposing variables.1-3 Furthermore, human papillomavirus (HPV) infection is connected to an increasing frequency of oropharyngeal malignancies. Depending on the region of the initial tumour, TNM staging, predicted
oncological and functional results, and treatment toxicities. HNSCC treatment typically includes surgery, radiation (RT), and chemotherapy (CT). Early-stage disease may usually be treated with a single modality, whereas advanced stages require a multimodal approach. Integration of surgery, RT, and CT has become the standard of therapy in recent years.\(^4\)\(^6\) HNSCC is the world's sixth most frequent cancer, with over 600,000 cases diagnosed each year. Approximately two-thirds have advanced-stage illness. The 5-year survival rates for these patients are around 50%. Despite improvements in conventional therapy, survival rates for HNSCC have remained essentially stable over the last three decades, despite the intrinsically good prognosis in HPV-positive individuals. Advanced HNSCC disease necessitates strong chemoradiation, which frequently causes severe side effects (xerostomia, dysphagia, etc.) that limit post-treatment quality of life.\(^7\)\(^9\) Furthermore, currently available cytotoxic chemotherapy drugs are non-selective and have high toxicity. As a result, novel drugs that may be safely integrated into current therapy regimens to improve both tolerance and efficacy are urgently needed. When combined with CT or RT, the sole FDA-approved EGFR-targeted drug, cetuximab, improves overall survival (OS) for HNSCC patients. However, the RR of cetuximab as a single drug is generally less than 15%. As a result, innovative molecular therapies for HNSCC are also required to combat drug resistance.\(^10\)\(^12\) However, there is still a gap in the management of metastatic disease. Although the progress of immune checkpoint inhibitors has resulted in much better results, only a tiny percentage of patients benefit. The majority of individuals with recurrent and/or metastatic HNSCC continue to have a dismal prognosis. This has prompted extensive research into new biomarkers and biomarker-based therapeutics. Adaptive cellular therapy and therapeutic vaccinations are two new treatment alternatives on the horizon.\(^13\)\(^15\) In this review, we highlight the most recent developments in the field of HNSCC as well as the research's future directions.

**EXISTING TREATMENT**

**Conventional treatment**

Surgery, Radiation Therapy, and Chemotherapy are the most common therapy for HNSCC. Surgery is a common treatment for HNSCC, and it is often determined by the anatomical location and extent of the tumour, as well as the aim to preserve organ function. Advances in reconstruction techniques have made it possible for patients who require large surgical resections in LA-HNSCC to have significantly improved functional outcomes, even in cases where organ-preserving treatment has failed. When residual disease is detected, neck dissection is usually performed as part of main surgical care or after chemoradiotherapy. Sentinel lymph node biopsy is receiving a lot of attention these days.\(^16\)\(^19\) Moreover, advances in minimally invasive endoscopic laser or robotic techniques have reduced postoperative complication and is related to a better organ and functional preservation. Nevertheless, even continued evolution in surgical techniques, surgery alone is accompanied by a high risk of relapse in LA-HNSCC, and combination with other treatments is usually indicated. RT alone for early stage HNSCC can give rise to high tumor control and cure rates, but for LA-HNSCC, it is an integral part of primary or adjuvant treatment. Intensity-modulated radiation therapy (IMRT) represents an improvement of high-precision radiation in three dimensions that delivers radiation more precisely to the tumor while relatively sparing the surrounding normal tissues.\(^20\)\(^23\)

**RECENT ADVANCES IN CHEMOTHERAPY**

**EGFR biology and EGFR-targeted therapy**

EGFR/human EGFR 1 (HER1)/ErbB1, HER2/neu/ErbB2, HER3/ErbB3, and HER4/ErbB4 are transmembrane glycoproteins that belong to the EGFR tyrosine kinase family. Extracellular ligand-binding domains, membrane-spanning domains, and cytoplasmic tyrosine kinase domains are found in all four members of the family. Many human epithelial malignancies, including HNSCC, have been
found to have abnormal EGFR expression or activity. Activation of EGFR by various ligands causes homo- or heterodimerization of EGFR with another HER family receptor, and autophosphorylation of tyrosine residues causes downstream signalling cascades to be activated including the well-known MAPK, phosphatidylinositol-3-kinase (PI3K)/Akt and STAT pathways that control gene transcription, cell proliferation and anti-apoptotic signals. These ligands are classified into three categories. The first group, which comprises epidermal growth factor (EGF), TGF-, and amphiregulin, binds to EGFR specifically. The second group, which comprises epiregulin, -cellulin, and heparin-binding EGF, binds to both EGFR and HER4. The neuregulins 1–4 make up the third group, which solely binds to HER3 and HER4. There is no known ligand for HER2. Although HER3 is the sole member of the family without an intrinsic kinase activity, downstream signalling is easily accomplished by heterodimerization. Despite the fact that clinical trials of EGFR-targeted medicines have rarely shown a link between EGFR overexpression and EGFR-targeted therapy efficacy, EGFR-targeting medicines are now classed as either mAbs or TKIs. Intravenously given monoclonal antibodies (mAbs) specifically bind to the EGFR and prevent ligand-binding driven receptor activation. Oral TKIs can block downstream signalling by reversibly or irreversibly inhibiting ATP binding to the intracellular domain of EGFR.

mAbs

Zalutumumab is a human IgG1 anti-EGFR mAb with a high affinity for eliciting ADCC. Because it is entirely human-derived, it is expected to have a lower immunogenicity profile than cetuximab, reducing the risk of hypersensitivity events and jeopardising treatment efficacy over time. In patients with incurable R/M HNSCC, zalutumumab + best supportive care (BSC) was linked with a longer PFS than BSC alone (median 9.9 vs 8.4 weeks; p = 0.0012) in a Phase III trial. However, the study’s goal of enhancing OS was not met (median 6.7 vs. 5.2 months; p = 0.0648). A Phase III trial to determine whether zalutumumab as a component of primary curative RT or CRT increases locoregional control in HNSCC patients is ongoing (NCT00496652).

Panitumumab is a human IgG2 anti-EGFR monoclonal antibody that may not trigger ADCC as strongly as cetuximab, therefore lowering the risk of life-threatening hypersensitivity events. Panitumumab with paclitaxel, carboplatin, and intensity-modulated RT were found to be a tolerable combination in a Phase I investigation and were linked with at least a partial response (PR) in all 19 LA-HNSCC patients [60]. Panitumumab with standard platinum-based CT versus CT alone in R/M HNSCC did not increase median OS (11.1 vs 9.0 months; p = 0.14) but did enhance median PFS (5.8 vs 4.6 months; p = 0.004) in a Phase III trial (SPECTRUM).

Nimotuzumab, like cetuximab and panitumumab, is a humanised anti-EGFR mAb with a lower risk of skin harm. Unlike other anti-EGFR antibodies, nimotuzumab’s inherent features necessitate bivalent binding for sustained attachment to the cellular surface, allowing it to target cells with moderate-to-high EGFR expression. Because their higher affinity constants lead to larger toxicities, cetuximab and panitumumab have high avidity target binding for normal cells with modest EGFR expression. Duligotuzumab (a human IgG1 anti-EGFR/HER3 mAb, NCT01577173) [66,67], a dual-targeting anti-EGFR mAb that concurrently blocks two receptors, is being examined in early phase trials to overcome resistance to cetuximab. While these emerging anti-EGFR mAbs are being studied in the hopes of improving outcomes or reducing toxicity in HNSCC, there is no preclinical or clinical evidence that they are superior to cetuximab at this time.

TYROSINE KINASE INHIBITORS

Unlike the mAbs, the TKIs have been developed to target the tyrosine kinase domain of EGFRs and to inhibit downstream signaling, eventually blocking the proliferation of tumor cells.
Reversible EGFR TKIs

Gefitinib is a reversible EGFR TKI that is taken orally. It was the first TKI to enter Phase III testing in HNSCC. It is unlikely to be further developed, however, given to recent unfavourable trial results. In a Phase III trial, 486 recurrent HNSCC patients were given either CRT or surgery and were given either gefitinib 250 or 500 mg/day or methotrexate 40 mg/m2/week. The RRs for gefitinib 250, 500 mg/day, and methotrexate were 2.7, 7.6, and 3.9 percent, respectively, with no significant differences between the two doses of gefitinib or methotrexate. When compared to methotrexate, neither dose of gefitinib was linked with enhanced survival.41

Although an unanticipated subset analysis revealed that gefitinib increased survival in patients younger than 65 years (median 7.6 vs 5.2 months; p = 0.04), there was no change in OS (7.3 months docetaxel/gefitinib vs 6.0 months docetaxel/placebo). Another oral, small-molecule, reversible EGFR TKI that has shown success in patients with HNSCC is erlotinib. Erlotinib as monotherapy in R/MHNSCC exhibited tolerability and antitumor efficacy (overall objective RR was 4.3 percent) in an early Phase II trial. However, another randomised Phase II trial compared CRT plus erlotinib to CRT alone and found that the inclusion of erlotinib did not improve complete response (CR) or progression-free survival (PFS). Moreover, two Phase III trials of erlotinib, one as a component of first-line standard platinum containing CT for advanced HNSCC (NCT00448240) and the other as maintenance monotherapy after CRT or RT alone for resected HNSCC (NCT00412217), were terminated early for low accrual.42

Dual and pan-HER TKIs

The reduced effectiveness of EGFR-targeted mAbs or TKIs may be due to heterodimerization of EGFR with other members of the HER family. As a result, the capacity to block more than only EGFR could be of relevance.43

Lapatinib is a reversible dual EGFR and HER2 TKI that is taken orally. In 67 unresected LA-HNSCC patients, a randomised Phase II study assessed the activity and safety of CRT plus lapatinib followed by lapatinib maintenance treatment, and found that lapatinib combined with CRT is well-tolerated, with a 53 percent increase in CRR (53 vs 36 percent) at 6 months post-CRT and a median PFS (55 vs 41 percent) at 18 months post-CRT compared.44

Another Phase II trial found that a four-week course of lapatinib monotherapy did not promote tumour apoptosis but did demonstrate clinical effectiveness in LA-HNSCC (objective RR was 17 versus 0% placebo). In contrast, a recent Phase II trial of lapatinib as monotherapy in R/M HNSCC found no CR or PR in either EGFR inhibitor-naive or refractory patients.45

Afatinib is a TKI that inhibits EGFR (including EGFR vIII), HER2, and HER4 kinases in an irreversible manner. 124 patients with R/M HNSCC who had failed platinum-based therapy were randomised to receive afatinib 50 mg/day or cetuximab 250 mg/m2/week in an open-label, randomised Phase II trial conducted in 43 locations.46

Afatinib’s antitumor activity was equivalent to that of cetuximab, with tumour shrinkage of 10.4 percent versus 5.4 percent, ORR 16.1 percent versus 6.5 percent, and disease control rates of 50 percent versus 56.5 percent, respectively. The median OS was equally comparable (35.9 vs 47.1 weeks, p = 0.78). In stage II, the disease control rate was 38.9% with afatinib and 18.8% with cetuximab, indicating that sequential treatment with afatinib and cetuximab provided long-term therapeutic benefit with no cross-resistance.47

Other Targeting Agents Investigated To Overcome Egfr-Targeted Therapy Resistance

**c-MET**

c-MET is a transmembrane tyrosine receptor that is typically expressed on epithelial cells and can be activated by mesenchymal cells' secreted hepatocyte growth factor (HGF). When MAPK, PI3K,
STAT3, and NF-B are abnormally active, this epithelial–mesenchymal interaction promotes downstream signalling and is linked to tumour proliferation, invasion, and angiogenesis. HGF is the only known ligand that binds to c-MET. Ficlatuzumab is a humanised anti-HGF mAb that inhibits c-MET activation produced by HGF. To date, antitumoral activity has been proven in preclinical research and clinical trials. 48

Increased expression and activation of c-MET is linked to EGFR inhibitor resistance, radiation resistance, and cisplatin resistance when the MET oncogene is amplified. In 58–84 percent of HNSCC tumours, c-MET is overexpressed, and c-MET mutations have been found in HNSCC tumour tissues and cell lines. Foretinib is an oral c-MET and VEGF receptor 2 multikinase inhibitor (VEGFR2). Foretinib (240 mg/day) was given orally to 14 R/M HNSCC patients in a Phase II study. Fifty percent of patients had stable disease, 43 percent (6/14) had tumour shrinkage, and two patients had disease stability that lasted more than 13 months. 49

**IGF-1 receptor targeted agent**

When activated by either IGF or EGF, the IGF-1 receptor (IGF-1R) is overexpressed in HNSCC cells and may heterodimerize with EGFR, activating downstream signalling pathways involved in cell growth, proliferation, differentiation, anti-apoptotic signalling, and angiogenesis [89]. Elevated IGF-1R expression has been linked to the efficacy of gefitinib in HNSCC patients undergoing postoperative CRT. Although the IGF-1R has been implicated as a target for HNSCC treatment, Phase II trials of figitumumab (a completely human IgG2 subtype mAb targeting the IGF-1R) in incurable HNSCC with progressing illness on platinum-based therapy are currently underway. 50

**VEGF/VEGFR-targeted agents**

Angiogenesis is a process that is critical for primary tumour growth, cell proliferation, invasiveness, metastasis, and radio-resistance. Multiple growth factors, including the VEGF, are known to be secreted by cancer cells in hypoxic environments. The most significant member of the VEGF family, VEGF-A, regulates angiogenesis via attaching to the VEGFR1–3 receptors. VEGF and VEGFR expression in tumour tissue is linked to a worse prognosis in HNSCC. Currently, antibody-mediated inhibition of VEGF and small-molecule inhibition of VEGF tyrosine kinases are the two most common methods for inhibiting angiogenesis. 51

Bevacizumab is a humanised anti-VEGF monoclonal antibody that binds to all five isoforms of VEGF, lowering total circulation VEGF levels. The addition of bevacizumab to cisplatin + IMRT did not increase toxicity in LA-HNSCC patients in a Phase II trial. The combination of bevacizumab and cetuximab was well tolerated and demonstrated some effectiveness in 46 R/M HNSCC patients in another Phase II trial. The ORR, DCR, median PFS, and OS were 16, 73 percent, 2.8 months, and 7.5 months, respectively. However, significant bleeding events occurred in 15% of patients in another Phase II trial with the addition of bevacizumab to pemetrexed in 40 R/M HNSCC patients, and two patients died. 52

**Src kinases inhibitor**

Src kinases are intracellular tyrosine kinases that activate the STAT family of transcription factors, particularly STAT3, to regulate cellular proliferation and survival. Inhibition of c-Src inhibits invasion, induces apoptosis [108], blocks DNA repair and EGFR nuclear translocation, and sensitises HNSCC cell lines to radiation and enhances EGFR inhibition in preclinical HNSCC models. Dasatinib is a Src kinase inhibitor that is a tiny chemical. Dasatinib monotherapy, on the other hand, failed to show efficacy in a Phase II trial with R/M HNSCC. 53 Although two individuals (16.7 percent) had stable illness at eight weeks, there was no OR among the 12 patients assessed. Dasatinib was added to cetuximab in recurrent HNSCC patients who had previously received cetuximab-containing curative therapy in a Phase II trial (NCT01488318), to cetuximab and RT cisplatin in LA HNSCC patients in a...
Phase I/II trial (NCT00882583), and to erlotinib in a biomarker-focused evaluation for HNSCC patients with planned primary or salvage.54

**PI3K/Akt/mTOR pathway inhibitors**

Independent of EGFR activation, PI3K/Akt/mammalian target of rapamycin (mTOR) signalling plays a critical role in the carcinogenesis of several human malignancies, including HNSCC. As a result, changes in this pathway may play a role in resistance to anti-EGFR therapy, making it a promising target for molecular-based pharmacological therapies. In the setting of R/M HNSCC, three Phase II studies with PI3K inhibitors are currently underway: BKM120 as monotherapy in patients with platinum-refractory R/M disease (NCT01737450), BYL719 plus cetuximab versus cetuximab alone (NCT01602315), and PX-866 plus docetaxel versus docetaxel alone (NCT01204099).55

The atypical serine/threonine kinase mTOR, which governs cell development by coordinating growth factor and nutrient signalling, is one of Akt's key downstream effectors. Preclinical evidence in HNSCC models suggests that temsirolimus, when coupled with EGFR inhibitors or bevacizumab – cetuximab – irradiation, has a synergistic effect. However, after enrolling 12 patients, a Phase II research assessing the combination of erlotinib and temsirolimus in platinum-refractory R/M HNSCC patients was halted due to toxicity. Other trials with temsirolimus (NCT01256385) and another mTOR inhibitor, everolimus (NCT01283334, NCT00942734), as monotherapy or in combination with other treatments (NCT01283334, NCT00942734).52

**Gene therapy**

Developing more efficient anticancer therapies and decreasing treatment-related toxicity by targeting the particular genetic changes responsible for carcinogenesis and cancer progression is an appealing technique. Gene therapy is usually administered locally, and HNSCC is an excellent candidate for it because lesions are easily accessible for injection or application of the agent. Mutations of tumour suppressor genes such as TP53, the retinoblastoma gene, p16 (CDKN2A), and PTEN have been described in head and neck cancer. The protein p53 plays a vital role in the cell cycle and apoptosis, and has a high rate of TP53 mutation (69.8%).53

In 2003, the State FDA of the People's Republic of China (SFDA) approved Gendicine (SBN-1) as the first Adp53-based gene therapy medication in the world for the treatment of HNSCC, and it was formally released in 2004. It’s a recombinant human serotype 5 adenovirus with a human wild-type p53 expression cassette in the E1 region that's been studied in clinical studies for the treatment of cancer patients.54 The expressed wild-type p53 gene's anticancer effects include initiating apoptotic pathways, activating immune response factors such as natural killer (NK) cells, suppressing DNA repair and anti-apoptotic capabilities, and limiting the transcription of survival signals. In a Phase I clinical trial, 12 patients with advanced laryngeal carcinoma received Gendicine plus surgery. The relapse rate in the Gendicine + surgery arm was 0% after three years, compared to 30% in the surgery-alone arm. In three Phase II/III clinical trials, Gendicine was found to have synergistic benefits with RT in HNSCC.55

**Immunotherapy**

Immunotherapy is a potential topic for HNSCC treatment since it mobilises the immune system to target cancer cells that produce tumor-specific antigens while having minimal side effects on normal tissue. The immune system of HNSCC patients is frequently inhibited, with dysregulation of immune competent cells and cytokines. Because innate and adaptive immunity play such a crucial part in HNSCC pathogenesis, immunotherapeutic methods are likely to be successful.56 Immunotherapy is more precise than traditional chemotherapies, is often less toxic, and has the potential to induce memory responses that could provide long-term tumour immune surveillance. Specific and non-specific
immunotherapies are two types of immunotherapies. Non-specific immunity includes antigen-unspecific macrophages, dendritic cells (DC), NK cells, and a variety of factors and cytokines, while specific immunity includes T cells and antibodies precisely recognising and engaging a target. HNSCC patients have been given a variety of immune-modulating drugs to try. These include the non-specific immune agents listed below that target specific tumour antigens, as well as vaccination candidates based on various antigenic triggers.\textsuperscript{57}

**Anti-programmed cell death -1 antibody:**

PDL-1 (programmed death ligand-1) is a B7 superfamily ligand that suppresses T-lymphocyte activity and is expressed on tumour cells. The receptor for PDL-1, programmed cell death-1 (PD-1), is expressed preferentially on apoptotic cells. TCR-mediated IL-2 activation and T-cell proliferation signal are inhibited when PDL-1 binds to PD-1 on T cells. This dynamic also includes tumor-infiltrating lymphocytes, which represent the host's immunological response to a malignant tumour. PDL-1 expression in HNSCC cells was found to be linked to a reduction in intratumoral TILs. In R/M platinum-refractory HNSCC, a Phase III trial comparing this new anti-PD-1 (nivolumab) to cetuximab/methotrexate/docetaxel is underway.\textsuperscript{58}

**Other immunotherapeutic agents:**

HNSCC is also being treated with various immunotherapeutic drugs. In resectable HNSCC, a Phase II trial (NCT00210470) found that a multi-cytokine immunotherapy regimen (IRX-2) administered in conjunction with cyclophosphamide, indomethacin, and zinc, followed by surgery, was well tolerated. In addition, therapeutic vaccination techniques such as peptide-based vaccines (NCT00257738, NCT00704041), a DNA vaccine (NCT02163057), and a DC vaccine are being tested in several ongoing Phase I–II trials (NCT00404339). In HNSC, the best effective immunotherapeutic regimen is still being determined.\textsuperscript{59}

**PEMBROLIZUMAB**

Pembrolizumab is a humanized monoclonal antibody that binds to the PD-1 receptor and prevents it from interacting with its ligands, PD-L1 and PD-L2. It has a molecular weight of 140 kDa and is an IgG4 kappa immunoglobulin. Pembrolizumab is a drug that is given intravenously and has a high bioavailability. Pembrolizumab has a low clearance rate of 0.22 L/day, which is comparable to other monoclonal antibodies. It has a distribution volume of 6 L, showing that it has a limited dispersion beyond extracellular space, indicating that the drug is available to bind its target on circulating T-cells. Pembrolizumab has a 27.3-day elimination half-life.\textsuperscript{60}

These findings are similar to those of other monoclonal antibodies in terms of pharmacokinetics. With a repeated dose every 3 weeks and a modest systemic accumulation of 2.2-fold, pembrolizumab takes 129 days to reach steady-state concentration. Elossaiss-schaap et al showed a linear clearance of pembrolizumab at dosages between 1 and 10 mg/kg every 3 weeks in a model-based study of KEYNOTE-001. Ex vivo simulations revealed that target engagement saturation began at a dose of 1 mg/kg every 3 weeks, and that a steady-state dose of 2 mg/kg every 3 weeks is required to achieve 95 percent target engagement. In randomised comparative pembrolizumab dose levels, the activity of 2 mg/kg every 3 weeks has been validated. Because monoclonal antibodies like pembrolizumab are eliminated through protein catabolism in several tissues, their clearance is not dependent on a single organ.\textsuperscript{61}

**REFINEMENTS OF INVESTIGATIONS**

Improvements in diagnostic techniques may be useful in avoiding futile surgical procedures, for example, endoscopies and examinations under general anesthesia and elective and planned neck dissections.
SENTINEL NODE BIOPSY
Because the condition of the cervical lymph nodes is the single most important tumor-related prognostic factor, knowing the presence of lymph node metastases is essential for optimal treatment planning. Patients with clinical lymph node metastases, of course, require therapy, the most common of which is a neck dissection. If the neck is clinically negative, however, you can choose between elective therapy and waiting it out. A meta-analysis found that conventional imaging techniques such as computed tomography (CT), MRI, ultrasound, and notably ultrasound-guided fine needle aspiration cytology are more reliable than palpation for detecting lymph node metastases, although probably not reliable enough to avoid elective treatment of the neck. Another meta-analysis found that fludeoxyglucose (FDG)-PET detected only 50% of occult lymph node metastases, confirming imaging tests' failure to record microscopic illness. The sentinel lymph node idea was developed in an attempt to more accurately locate lymph nodes that may contain metastases. The hypothesis of orderly dissemination of tumour cells inside the lymphatic system underpins the sentinel lymph node concept. The sentinel lymph node is the first lymph node in a regional lymphatic basin to receive lymphatic flow from a tumour. This lymph node is discovered using radioactive colloid in the sentinel lymph node method. This sentinel lymph node is examined in detail by histopathologically using stepped serial sectioning and immunohistochemistry.

TECHNICAL ADVANCES IN SURGERY
Recent technical advances include new operative techniques, instruments and surgical approaches.

RECONSTRUCTIVE TECHNIQUES
Several procedures have been developed to reconstruct faults and restore function and cosmesis following surgery. A range of reconstructive treatments are available depending on the location, size, and implicated tissues of the surgical lesion, as well as patient considerations. The arsenal of these reconstructions continues to grow. Others disclose adjustments or new reconstructive techniques, while some report on their series of a certain reconstructive approach. The radial forearm tenocutaneous free flap is described by Roh et al. as a method of soft palate rebuilding. They discovered that slinging the palmaris longus tendon across the levator and pharyngeal constrictor was effective.

Wreesmann et al. describe the use of a prefabricated revascularized bilaminar radial forearm free flap to close a tracheoesophageal fistula. The flap bulkiness for reconstruction was avoided by suturing and incubating a split skin graft on the inner surface of the free radial forearm flap, and a significant tracheoesophageal defect was repaired. In 25 patients with oropharyngeal deformities, Chepeha et al. describe an oropharyngoplasty with template-based repair of oropharyngeal malformations. The oropharynx's important functions are preserved by maximising the utilisation of local tissue in this repair. Velopharyngoplasty, hypopharyngeal closure, and base of tongue mounding are all included in this oropharyngoplasty. By reconstructing the velopharyngeal sphincter and improving the mobility of the base of tongue, the goal is to improve the contact with the remaining oropharyngeal tissue. The primary closure of the local tissues widened the defect, necessitating the resurfacing of the revascularized-free tissue. The retromolar trigone and buccal mucosa, nasal palate, and base of tongue were all built using an L-shaped flap template with additional subunits if needed. The speaking results were extremely good, and the swallowing results were comparable to those of the folded revascularized free flap and posterior pharyngeal flap methods.

ROBOTIC SURGERY
Transoral robotic surgery (TORS) is becoming more common in the treatment of head and neck cancer. It allows for greater visualisation and access to tumours through a less invasive, less morbid procedure, potentially leading to a better functional outcome. Improved optics, increased instrument degrees of freedom, and tremor modulation may be advantages over traditional surgery. Robotic surgery's rotational optics are superior to line-of-sight viewing with the operating microscope when compared to transoral laser surgery. However, it has been questioned if the advantages of robotic surgery exceed the high initial expenses of the robotic system as well as the costs of (disposable) tools. Despite the fact that experience is expanding, the overall number of cases recorded is still small when compared to surgical and nonsurgical series. As a result, its clinical utility has yet to be determined. TORS is unlikely to offer value if adequate conventional surgery is available. TORS, on the other hand, is likely to be very effective if radiotherapy can be avoided and maintained in reserve for eventual second primary tumours. The importance of proper triage cannot be overstated. To limit the proportion of cases that are terminated intraoperatively, a separate preoperative evaluation under general anaesthesia to assess for transoral exposure is recommended. Access is restricted for a variety of reasons. Because of the bulky design of the robotic arm, it is impossible to adequately retract peripheral soft tissue and access the lesion. Another factor that could limit frequent use is the entire operative duration as well as the time it takes to set up the operating room. Although total operating time appears to decrease with practise, it will almost always be lengthier than routine transoral resection.

**IMAGE-GUIDED SURGERY**

During surgical procedures, an intraoperative guiding system can help with orientation. However, its effectiveness in head and neck surgery is debatable. Homma et al. used this technique in five patients with sinonasal malignancies and concluded that it can enable the surgeon recognise target spots properly in real time, estimate the minimum accurate bone-resection line, and employ the most direct approach to reach the lesion during total maxillectomy. Vlantis et al. described the use of a frontal bone skull post for an image-guided system in patients who had recurrent nasopharyngeal cancer and underwent salvage nasopharyngectomy via various external routes. Mierzwa and Mueller presented a patient who had image-guided surgery with a navigation system and a thermoplastic mask to stabilise the moveable neck to remove a retropharyngeal metastasis. Image-guided surgery may be a realistic alternative for some patients with malignancies in difficult anatomical areas of the head and neck.

**PHOTODYNAMIC THERAPY**

Photodynamic treatment (PDT) is a type of treatment that involves combining a photosensitizing drug with laser light exposure to elicit phototoxic reactions that kill tumour cells. PDT is most effective for cancers that are small, confined, and superficial. Rigual et al. studied 26 individuals with oral cavity and laryngeal dysplasia, carcinoma in situ, and T1 cancer. A full response was reported in 24 (92%) of the patients, with three patients with oral dysplasia experiencing recurrence and requiring salvage treatment. PDT achieved local control in 21 (60%) of 35 patients with recurring or second main head and neck cancers who were unsuitable for conventional therapies. The tumours in these patients had a maximum thickness of 10 mm. Interstitial PDT is an alternative for deeper-seated malignancies. A prospective investigation of ultrasound-guided interstitial in 68 patients with various diseases (49 percent carcinomas) found that 75 percent of the patients had some radiological response. Only 16 percent of the patients had a significant response (a reduction of more than 50%). Interstitial PDT has a positive effect on squamous cell carcinoma. PDT is efficacious, decreases long-term morbidity, and does not jeopardise future therapy options for recurrent, residual, or second primary disease in carefully selected patients.

**ULTRASONIC SURGERY**

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Reliable hemostasis is required in head and neck surgery. The harmonic scalpel, which uses mechanical vibration for simultaneous coagulation and tissue cutting, is widely employed in thyroid surgery, where the technology is praised for its speed and efficiency. It is now commonly utilised in other surgical operations, such as parotidectomies, with similar effects. Pons et al. performed partial glossectomy effectively in 18 patients with T1 or T2 tongue cancer. With appropriate margins and no blood loss, an ultrasonic partial glossectomy was performed quickly and easily. The generator, notably the consumable ingredients, has a significant cost.80

MECHANICAL SUTURES
Pharyngeal restoration is traditionally done with manual (layered) sutures after a total laryngectomy. The most common complication following this treatment is the formation of a pharyngocutaneous fistula. The use of a stapled closed pharyngoplasty procedure appears to be effective and eliminates the possibility of wound contamination. After a total laryngectomy, Goncalves et al. compared manual versus mechanical suture healing. After mechanical suturing, the incidence of pharyngocutaneous fistula was much lower (2/30, 6.7%) than after manual suturing (11/30, 36.7%). Because mechanical suturing of the pharynx without accessing the mucosa may result in oncological criticism, blind tumour excision should be avoided.81-82

RECENT ADVANCES IN RADIOTHERAPY
Altered Fractionation
Traditionally, radiotherapy was administered in tiny doses five days a week for five to seven weeks. Various research have focused on changed fractionation schedules, in which two or three doses of radiation are provided daily, over the last decade. According to data from multiple studies, loco-regional management with adjusted fractionation offers better outcomes for individuals with advanced disease than the one-a-day strategy. When compared to conventionally fractionated radiation, the practical motivation for a changed fractionation scheme is to raise the biological dosage without raising the risk of late normal tissue damage.83

Three-Dimensional Conformal Radiotherapy (3D-CRT)
Traditionally, radiotherapy was administered in tiny doses five days a week for five to seven weeks. Various research have focused on changed fractionation schedules, in which two or three doses of radiation are provided daily, over the last decade. According to data from multiple studies, loco-regional management with adjusted fractionation offers better outcomes for individuals with advanced disease than the one-a-day strategy. When compared to conventionally fractionated radiation, the practical motivation for a changed fractionation scheme is to raise the biological dosage without raising the risk of late normal tissue damage. The tumour volume and regions of interest may now be viewed in three dimensions, allowing for the best beam configurations to adapt the radiation dose to the tumour while excluding the nearby normal organs to the greatest extent possible.85-87

Intensity-Modulated Radiation Therapy (IMRT)
The anatomy of the head and neck is extremely convoluted, with bony structures, soft tissues, and air cavities all crammed into a compact space. The organs that are at risk are frequently located near to the target volume, which has an uneven shape. Partially reducing the volume of irradiated normal tissue, as afforded by 3D-CRT, may not always minimise the risk of late toxicity. IMRT is a type of 3D-CRT that combines many intensity-modulated (radiation intensity varies within each beam) beams to achieve a highly conformal dose distribution. The overall process of IMRT and 3D-CRT is very similar; however, IMRT was made possible by two technological advances: the introduction of computer-controlled multileaf collimators and the development of computerised optimization, or “inverse planning,” which
determines the intensity of the beams required to meet a set of dose constraints. IMRT can be given via tomotherapy or traditional multileaf collimators at preset gantry angles (discussed later). IMRT enables for more conformal dose distribution and the creation of plans with the goal of conformal avoidance of vital organs at risk, allowing for tumour dosage escalation.\textsuperscript{88-90}

**Stereotactic Radiation**

The delivery of a significant radiation dose in a single fraction is referred to as stereotactic radiation, also known as stereotactic radiosurgery (SRS). The essential premise is that numerous low-dose radiation beams are administered in a way that permits them to intersect only at the target lesion, delivering a significant dosage precisely to the target while sparing surrounding structures. The second concept of SRS is that the targeted cellular effects are not dependent on cell cycle phase. The dose, when administered in single fractions, delivers a level of photon energy that causes considerable damage, resulting in tumour cell death independent of cell cycle phase and, unlike traditional radiation, does less damage to normal tissue in the surrounding area. As a result, radiosensitivity no longer applies in terms of the proportion of cells in mitosis having condensed DNA.\textsuperscript{91}

**CONCLUSION**

HNSCC’s management is rapidly changing. The use of concurrent systemic medicines, as well as continued technological developments in surgery and radiotherapy, have all contributed to considerable improvements in outcomes for patients with non-metastatic illness. However, there are still substantial side effects. Furthermore, most patients with R/M HNSCC continue to have a dismal prognosis. Although immunotherapy has been shown to produce long-term results, this advantage is only found in a small proportion of individuals. Immunotherapy, vaccinations, cellular treatment, and the optimization of biomarker integration are all promising approaches for furthering the research.

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