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Contemporary advances in head and neck oncology: A review

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Abstract:
Head and neck oncology has evolved through advances in surgical technique, radiotherapy, systemic treatment, molecular diagnostics and supportive care. Transoral robotic surgery (TORS), exoscopic visualization, augmented-reality navigation and fluorescence-guided margin assessment are being evaluated or used in selected clinical settings, but the strength of evidence and clinical availability differ across technologies. Molecular profiling and immune checkpoint inhibitors have changed treatment for defined patient groups, while adaptive radiotherapy, liquid biopsy and artificial-intelligence applications continue to develop. This review summarizes selected clinical trials, guidelines and translational research relevant to contemporary head and neck cancer care, emphasizing clinical applicability, limitations and areas where further validation is required.

Keywords: Head and neck cancer, oral squamous cell carcinoma, transoral robotic surgery (TORS), immunotherapy, molecular biomarkers, radiotherapy, artificial intelligence, multidisciplinary care

Background:
Head and neck malignancies comprise cancers arising in several anatomical subsites, including the oral cavity, oropharynx, larynx, hypopharynx, nasopharynx and salivary glands; epidemiology and treatment vary by site **[1, 2]**. Oral squamous cell carcinoma (OSCC) accounts for the large majority of oral cavity malignancies, although the exact proportion depends on case definitions and the population studied **[3, 4]**. Cervical nodal involvement is an important prognostic factor, alongside primary-tumor stage, depth of invasion, margin status, extranodal extension, perineural and lymphovascular invasion, distant disease and patient-related factors **[5].** Incidence and mortality differ across countries and socioeconomic settings, reflecting differences in exposure, early detection and access to treatment **[6].** Major risk factors for oral cavity squamous cell carcinoma include smoked and smokeless tobacco, areca nut and betel quid and alcohol; combined exposures may increase risk **[7, 8].** HPV is particularly relevant to a subset of oropharyngeal cancers and should not be treated as an equivalent risk factor for conventional oral cavity OSCC. Other factors vary by site and include ultraviolet exposure for lip cancer and inherited cancer-predisposition syndromes. Oral potentially malignant disorders require careful clinical assessment and histopathological evaluation when indicated; the malignant potential of individual disorders differs and oral lichen planus should be discussed with appropriate diagnostic and classification nuance **[9].** Therefore, it is of interest to examine the selected contemporary advances and their clinical limitations.

Carcinogenesis and genomic instability:
Oral carcinogenesis is a multistep process involving somatic mutations, chromosomal and copy-number alterations and epigenetic changes **[9, 10].** Alterations affecting tumor-suppressor pathways, including TP53 and CDKN2A and dysregulation of signaling pathways such as EGFR and PI3K/AKT/mTOR have been described in OSCC **[10, 11].** These mechanisms provide a biological rationale for investigation of targeted approaches, but the presence of a pathway alteration does not itself establish that a corresponding targeted treatment is clinically effective in an individual patient.

Epidemiological focus: status of oral cancer in India:
India has a substantial oral cancer burden, with important contributions from smokeless tobacco, areca nut products and smoking exposures **[12].** The distribution of disease varies within and between states and populations; claims comparing specific states should be based on population-based cancer registry data and clearly defined incidence measures rather than extrapolated from a general review. Tobacco-related carcinogens and repeated mucosal exposure are consistent with the concept of field cancerization, which is relevant to second primary tumors and long-term surveillance **[12].**

Diagnostic paradigms: from clinical screening to molecular biomarkers:
Earlier-stage diagnosis is generally associated with less extensive treatment and better outcomes, but survival estimates vary by anatomical subsite, stage, HPV status where relevant, comorbidity and treatment; a single figure such as 90% should not be generalized to all oral cancers **[13].** Clinical assessment includes systematic visual examination and palpation of the oral cavity and appropriate examination of regional lymph nodes. Persistent suspicious lesions, including erythroplakia, indurated or non-healing ulcers, unexplained masses, or persistent swallowing symptoms, require timely specialist assessment and tissue diagnosis when indicated **[14].** Molecular profiling and liquid biopsy are active areas of investigation, but their clinical roles differ by tumor type and treatment setting **[15].** Multigene sequencing may be appropriate in selected advanced cancers when results could inform an approved or investigational treatment; it is not required routinely for every patient with OSCC **[16, 17].** Studies have detected tumor-associated alterations and HPV in saliva and plasma, but these findings should not be interpreted as proof that salivary or plasma ctDNA is already validated for routine minimal-residual-disease surveillance or recurrence detection in all oral cavity cancers **[18].** TMB, mismatch-repair deficiency and inflammatory measures such as NLR have different evidence bases and should not be presented as interchangeable or universally validated predictors of immunotherapy response**.**

Historical evolution of oral cancer management:

The development of modern oral cancer surgery involved a gradual transition toward systematic oncologic resection, improved neck-dissection techniques, reconstruction and multimodal treatment **[19].** Historical descriptions should be interpreted in their context and should avoid attributing a single modern surgical principle to one individual unless the cited historical source supports that attribution **[20].**

Treatment determinants and multidisciplinary decision-making:

The ultimate objective of oral and maxillofacial oncologic therapy is to achieve complete locoregional eradication while preserving or restoring speech, deglutition, airway protection and facial cosmesis **[21].** Contemporary therapeutic decision-making is governed by three primary domains: tumor characteristics, patient-related factors and institutional physician-related capabilities **[22].** Tumor-related characteristics encompass the primary anatomical subsite, TNM staging, proximity to cortical bone (mandible/maxilla), depth of invasion (DOI), perineural invasion (PNI), lymphovascular invasion (LVI) and cervical lymph node status (including extranodal extension) **[23].** Standardized TNM staging facilitates risk stratification and international research comparisons **[24];** levels I, II and III cervical lymph nodes present the highest metastatic risk for oral cavity carcinomas, whereas levels II, III and IV are at highest risk from carcinomas of the oropharynx, hypopharynx and larynx **[25].** Patient-related factors include chronological and physiological age, underlying cardiopulmonary comorbidities, nutritional status and lifestyle habits such as active tobacco and alcohol consumption. Importantly, advanced chronological age alone does not contraindicate curative surgical resections or microvascular reconstructions in physiologically fit individuals **[26],** although severe systemic comorbidities significantly influence tolerance to radical multimodal interventions **[27].** Physician- and center-related factors depend upon an integrated Multidisciplinary Team (MDT) framework encompassing ablative and reconstructive head and neck surgeons, radiation oncologists, medical oncologists, specialized nursing, maxillofacial prosthodontists and speech/swallowing pathologists to ensure optimal oncologic and functional outcomes **[28]**.

Scientific developments in head and neck surgery:

Surgical technologies under evaluation or in selected use include exoscopic visualization, augmented-reality navigation and fluorescence-guided approaches **[29].** Exoscopes can provide magnified visualization in selected operative settings, while augmented-reality systems attempt to align preoperative imaging with the operative field **[30].** These technologies may improve visualization or procedural planning, but registration error, workflow complexity, cost, learning curves and limited comparative outcome data constrain broad claims of superior precision or improved survival. TORS provides access to selected anatomically challenging sites, particularly the oropharynx and base of tongue, in appropriately selected patients **[31].** Single-port systems have been studied for feasibility and safety and transoral approaches to selected retropharyngeal nodes have been described; neither should be generalized to all head and neck tumors or assumed to eliminate morbidity in every case. Fluorescence-guided techniques, including indocyanine green and targeted optical probes, are being investigated for tumor visualization and margin assessment, but performance depends on the agent, tumor biology, tissue depth and validation method **[32].**

Systemic frontiers: immunotherapy, targeted agents and de-escalation:

Systemic treatment has an established role in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), with regimen selection depending on disease setting, prior therapy, performance status and biomarkers such as PD-L1 combined positive score (CPS) where relevant **[33].** KEYNOTE-048 supports pembrolizumab-based first-line options in defined recurrent/metastatic settings, while CheckMate 141 evaluated nivolumab after platinum-based treatment **[34].** Not all checkpoint-inhibitor trials have been positive: the EAGLE and JAVELIN Head & Neck 100 studies did not establish benefit for their tested regimens in the studied settings **[35].** EA3202 is a trial evaluating treatment options after progression on checkpoint inhibition and should be described as a study protocol, not evidence of established efficacy**.** Consensus statements and clinical-practice guidelines should inform, but not replace, patient-specific multidisciplinary decisions **[36].** Beyond classical PD-1/PD-L1 single-agent checkpoints, modern systemic strategies are evolving to target primary and acquired therapeutic resistance recent evaluations highlight novel immune checkpoint combinations (such as LAG-3 and TIGIT inhibitors), bispecific antibodies (including EGFR-targeted petosemtamab), antibody-drug conjugates (ADCs) and emerging nanomedicines or PROTAC-based molecular degraders these modalities aim to overcome primary non-response and secondary immune evasion in advanced and recurrent/metastatic settings, though rigorous clinical trial validation remains ongoing **[37].** Treatment de-escalation is an area of investigation, especially in carefully selected HPV-positive oropharyngeal cancer, where reducing late toxicity is an important goal **[38].** ECOG-ACRIN 3311 provides phase II evidence relevant to risk-stratified postoperative treatment in selected patients, whereas PATHOS and other studies evaluate treatment strategies and should not be described as proof of universal efficacy or as a basis for extrapolation to conventional oral cavity OSCC **[39].** The AVOID study examined elective nodal-only radiotherapy in a defined risk group; conclusions should remain limited to the studied population and protocol **[40].** De-escalation should be undertaken only in settings supported by appropriate evidence and guideline-based decision-making.

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Table 1: Summary of pivotal clinical trials in systemic therapy and treatment de-escalation for head and neck carcinoma

Trial Name	Target Population	Investigational Interventions vs. Comparator	Primary Outcome(s)	Key Clinical Takeaway & Relevance	Citation
KEYNOTE-048	Untreated recurrent or metastatic (R/M) HNSCC	Pembrolizumab monotherapy• Pembrolizumab + platinum/5-FUvs. EXTREME regimen (cetuximab + platinum/5-FU)	Overall Survival (OS) in PD-L1 CPS ≥20, CPS ≥1 and total population	Established first-line standard of care: pembrolizumab monotherapy improves OS in PD-L1 CPS ≥1; pembrolizumab plus chemotherapy improves OS across the total population with lower toxicity than the EXTREME regimen.	**[41]**
CheckMate 141	Platinum-refractory recurrent or metastatic (R/M) HNSCC	Nivolumab monotherapy vs. Investigator's Choice (single-agent docetaxel, paclitaxel, or methotrexate)	Overall Survival (OS)	Confirmed long-term survival advantage and favorable safety profile of PD-1 blockade after platinum failure, solidifying second-line immunotherapy.	**[42]**
EAGLE	Platinum-refractory recurrent or metastatic (R/M) HNSCC	• Durvalumab monotherapy• Durvalumab + tremelimumabvs. Standard of Care chemotherapy	Overall Survival (OS)	Negative trial; did not demonstrate statistically significant improvement in OS over standard chemotherapy, underscoring that dual CTLA-4/PD-L1 blockade or anti-PD-L1 monotherapy cannot be assumed uniformly efficacious in this setting.	**[43]**
JAVELIN Head & Neck 100	Locally advanced (LA) unresected HNSCC (high/intermediate risk)	Avelumab (anti-PD-L1) + standard definitive chemoradiotherapy (CRT) vs. Placebo + standard definitive CRT	Progression-Free Survival (PFS)	Negative trial; concurrent addition of avelumab to definitive high-dose cisplatin-based chemoradiotherapy failed to improve PFS, demonstrating limits of extrapolating metastatic efficacy to primary concurrent CRT.	**[44]**
ECOG-ACRIN 3311	Resected intermediate-risk HPV-positive (p16+) oropharyngeal carcinoma (cT1–T2, cN1–N2b)	Transoral robotic surgery (TORS) + neck dissection followed by reduced-intensity adjuvant radiotherapy (50 Gy) vs. standard-dose adjuvant radiotherapy (60 Gy)	2-year Progression-Free Survival (PFS)	Phase II trial showing reduced-dose postoperative radiation (50 Gy) after primary TORS preserves excellent oncologic control while minimizing radiation-associated functional impairment in selected intermediate-risk HPV+ cases.	**[45]**

Adjuvant radiotherapy and delivery advances:

Post-operative radiotherapy, with or without concurrent systemic therapy, is considered according to pathological risk and multidisciplinary assessment. Involved margins and extranodal extension are important high-risk features; other indications depend on the full pathological profile and applicable guidelines **[43].** Post-operative radiotherapy commonly uses conformal techniques such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT). Proton therapy may be considered for selected patients when a meaningful dosimetric advantage is expected, but the clinical benefit, availability and cost-effectiveness depend on the indication and evidence base **[44]**. Adaptive radiotherapy is an evolving approach and should be discussed separately if retained as a central claim of the review. Post-operative dose and target volumes should be individualized according to pathology, surgical-bed anatomy, treatment intent and normal-tissue constraints. Regimens in the approximate 60–66 Gy range are used in many high-risk postoperative settings, but dose and concurrent systemic therapy are not universal and should follow site-specific guidelines and multidisciplinary review **[45].** Organs at risk include salivary glands, spinal cord, mandible and swallowing structures. Radiation-induced trismus (RIT) represents a severe and often irreversible late sequela that compromises speech, deglutition, oral hygiene and oncologic surveillance While maximal mouth opening (MMO) thresholds defining trismus vary across studies, an MMO of 35 mm or less is commonly utilized Mitigating RIT requires strict dosimetric sparing of the masticatory apparatus—including the pterygoid muscles, masseter muscles and temporomandibular joints—via conformal IMRT, VMAT, or proton beam therapy, combined with active physical therapy protocols **[46].**

Role of artificial intelligence in cancer care:

AI, machine learning and deep learning are being investigated across head and neck oncology, including image analysis, radiomics, segmentation, treatment planning and outcome prediction **[47]**. These applications differ substantially in maturity and validation. Broad reviews of AI in medical imaging do not independently establish performance for a specific oral lesion or nodal-metastasis task; claims about sensitivity, specificity, recurrence prediction, or immunotherapy response require task-specific studies and external validation. Important limitations include dataset shift, class imbalance, interpretability, bias, privacy, reproducibility and prospective clinical utility.

Immediate post-operative care and multidisciplinary rehabilitation:

Recovery after major ablative surgery and free-flap reconstruction benefits from coordinated perioperative care tailored to operative extent, comorbidities, airway needs, nutrition and reconstruction. Postoperative care may include regular assessment of flap viability, adjunctive Doppler monitoring where appropriate, protocol-driven airway management and early mobilization, multimodal analgesia, swallowing assessment, speech-language therapy and individualized nutritional support **[48]**. Given the significant impact of radiation-induced trismus on functional recovery and quality of life, preemptive jaw rehabilitation exercises initiated prior to or during radiation therapy are essential to preserve masticatory function and mouth opening **[49].** The overall postoperative and survivorship pathway should be adapted to local resources and the patient's clinical condition. ERAS pathways have been associated with improvements in selected

perioperative outcomes after head and neck free-flap reconstruction, although interventions and reported effects vary among studies and institutions **[50]**.

Conclusion:
Contemporary head and neck oncology combines established surgery, radiotherapy, systemic treatment and rehabilitation with emerging technologies such as robotic approaches, optical guidance, molecular profiling and AI. Their clinical value should be judged according to the quality of evidence, patient selection, safety, functional outcomes and cost and access considerations. Greater precision and organ preservation are important goals, but not every technological advance has yet demonstrated superior cancer control or quality of life.

Advancement of knowledge:
This review critically summarizes selected developments in head and neck oncology and distinguishes established treatment approaches from technologies and biomarkers that remain under evaluation. It emphasizes the importance of site-specific evidence, multidisciplinary decision-making, transparent reporting and patient-centered functional outcomes.

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[1] Kedar Saraf: Conceptualization, Data curation, Formal analysis, Project administration, Resources, Writing – original draft
[2] Anuja Saraf: Formal analysis
[3] Shital Nikam: Methodology, Writing – original draft (partially)
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[5] Anuja Ghule: Editing
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