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Original Research Article

Multidisciplinary Management of Oral and Maxillofacial Carcinomas: Surgical Perspectives and Outcomes

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Abstract: ***Background:*** Oral and maxillofacial carcinomas represent a significant global health burden with complex management challenges. This comprehensive review examines contemporary surgical approaches within a multidisciplinary framework. Accurate staging through the revised AJCC/UICC 8th edition system, integrating depth of invasion and extranodal extension, guides treatment planning. Preoperative assessment incorporating virtual surgical planning and nutritional optimization has demonstrated improved outcomes. Surgical management has evolved from radical approaches to selective, function-preserving techniques including transoral robotic surgery for appropriate candidates, while maintaining oncologic integrity. Contemporary reconstruction strategies emphasize functional outcomes through free tissue transfer and computer-aided design. The integration of radiation therapy and systemic treatments follows evidence-based risk stratification, with emerging roles for immunotherapy in specific molecular profiles. PD-L1 expression has emerged as a critical biomarker for immunotherapeutic selection, particularly in the recurrent/metastatic setting. Management algorithms are increasingly tailored to anatomical subsites, with consideration of molecular subtypes demonstrating distinct survival outcomes. Implementation challenges persist in resource-limited settings, necessitating tiered protocols and international collaborations. Future directions include refinement of predictive biomarkers, prospective validation of de-intensification strategies, and further development of tissue engineering approaches for reconstruction. The multidisciplinary model remains essential for integrating these evolving modalities to optimize both survival and functional outcomes in oral and maxillofacial carcinoma patients.

Keywords: Oral squamous cell carcinoma; Maxillofacial reconstruction; Virtual surgical planning; Immunotherapy; Molecular classification; Function preservation; Microvascular reconstruction; PD-L1; Sentinel lymph node biopsy; Multidisciplinary management.

INTRODUCTION

Oral and Maxillofacial Carcinomas: A Comprehensive Review

1. Introduction

Oral and maxillofacial carcinomas represent a significant global health burden, with approximately 377,713 new cases and 177,757 deaths annually worldwide [1]. These malignancies rank as the sixth most common cancer globally, with striking geographical variations in incidence rates ranging from 2.0 per 100,000 in Western Africa to 13.5 per 100,000 in South-Central Asia [1,3].

1.1 Epidemiology and Current Challenges

The epidemiological landscape demonstrates significant regional heterogeneity. While traditionally affecting older males with tobacco and alcohol histories, recent trends show alarming increases among younger populations and women, particularly in high-income countries [2]. Human papillomavirus (HPV) has emerged as a significant etiological agent for oropharyngeal carcinomas, creating distinct disease entities with different prognostic implications [3]. Five-year survival rates range from 30% to 80%, depending on anatomical subsite, stage at diagnosis, and treatment approach [4].

Major management challenges include late-stage diagnosis, with approximately 60% of patients presenting with advanced disease [5], high recurrence rates (25-50%) despite aggressive therapy [4], and second primary tumor development (3-7% annual risk) [5]. Treatment complexity involves balancing anatomical considerations with functional and aesthetic outcomes while integrating rapidly evolving therapeutic modalities [6].

1.2 Multidisciplinary Approach

The complexity of these carcinomas necessitates multidisciplinary team (MDT) management. Evidence demonstrates that MDT approaches improve diagnostic accuracy, treatment planning, and patient outcomes, with Chen et al. documenting 15% mortality reduction and 23% improvement in disease-free survival compared to traditional referral pathways [7]. Core teams typically include surgical oncologists, radiation oncologists, medical oncologists, pathologists, radiologists, and specialized support staff [8].

2. Classification and Staging

2.1 TNM Classification

The AJCC/UICC 8th edition (2018) introduced significant revisions reflecting evolving understanding of disease biology [9]. Key changes include incorporating depth of invasion (DOI) into T classification and extranodal extension (ENE) into N staging, with DOI each millimeter increase associated with 5-7% decreased survival [10]. HPV-mediated oropharyngeal carcinomas now have separate staging criteria recognizing their distinct biological behavior and superior outcomes [11].

2.2 Histopathological Classification

While squamous cell carcinoma accounts for 90% of cases, histopathological diversity carries important therapeutic implications [12]. Major subtypes include conventional SCC (75-80%), verrucous carcinoma (3-5%), basaloid SCC (5-10%), and spindle cell carcinoma (2-3%). Modern assessment incorporates standardized reporting of tumor grade, invasion pattern, perineural invasion, lymphovascular invasion, and tumor budding [16,17].

2.3 Imaging in Staging

Multimodality imaging is essential for accurate staging. MRI offers superior soft tissue contrast with >90% accuracy for local staging and excellent DOI assessment (±0.8mm) [13]. Functional sequences including diffusion-weighted imaging improve diagnostic performance for perineural spread and recurrence detection [14]. PET/CT revolutionized nodal and distant staging with >90% sensitivity and specificity, altering management in 15-20% of cases through detection of occult metastases and second primaries [20,21].

2.4 Molecular Classification

Comprehensive genomic profiling through The Cancer Genome Atlas revealed distinct molecular subtypes with therapeutic implications [15]. Key alterations include TP53 mutations (60-80%), CDKN2A alterations (55-70%), and PIK3CA mutations (10-30%) [15]. Four molecular subtypes (Atypical, Classical, Mesenchymal, Basal) demonstrate distinct clinical behaviors and treatment responses [16].

The immune microenvironment, evaluated through tumor-infiltrating lymphocytes and PD-L1 expression, provides additional prognostic information and predicts immunotherapy response [17]. Current recommendations support molecular testing for HPV status, PD-L1 expression, and comprehensive genomic profiling for recurrent/metastatic disease [18].

As precision medicine evolves, integration of molecular classification with traditional staging systems promises improved personalized treatment approaches for oral and maxillofacial carcinoma management.

3. Preoperative Assessment and Planning

Comprehensive preoperative assessment is fundamental to optimizing surgical outcomes for oral and maxillofacial carcinomas. Contemporary approaches integrate clinical evaluation, advanced imaging, virtual planning, and systematic optimization of patient-specific risk factors.

3.1 Clinical Evaluation

Thorough clinical assessment remains the cornerstone of preoperative planning, establishing baseline functional status and identifying risk factors that may influence treatment decisions [19]. Key components include:

Studies consistently demonstrate that comprehensive preoperative clinical assessment can identify modifiable risk factors in 30-45% of patients, allowing targeted interventions that reduce perioperative complications [20]. Standardized assessment protocols improve documentation consistency and communication across the multidisciplinary team [21].

3.2 Advanced Imaging Modalities

Modern imaging protocols enable precise tumor mapping, facilitate surgical navigation, and inform reconstruction planning. While the specific imaging modalities were detailed in Section 2.3, their application in preoperative planning deserves further discussion.

RESULTS

Table 1: Applications of Advanced Imaging Techniques in Preoperative Planning

Imaging Modality	Preoperative Planning Application	Clinical Impact
High-resolution CT	Bone invasion assessment, implant planning, airway evaluation	Guides extent of bony resection, identifies need for bone reconstruction
Contrast-enhanced MRI	Soft tissue invasion mapping, perineural spread assessment	Defines soft tissue resection boundaries, identifies involved neural structures
Angiography CT/MRI	Vascular mapping for reconstruction	Optimizes recipient vessel selection for microvascular reconstruction
Dual-energy CT	Metal artifact reduction, improved soft tissue contrast	Better visualization in patients with dental hardware
Functional MRI	Speech and swallowing function assessment	Informs functional preservation strategies
PET/CT	Synchronous primary detection, distant metastasis screening	Prevents futile surgery, guides extent of intervention
Intraoral 3D scanning	Dental occlusion, soft tissue topography	Digital dental rehabilitation planning

The integration of these imaging modalities into comprehensive diagnostic algorithms has demonstrated clinical benefit. A prospective study by Linz et al. [22] found that implementation of a standardized multimodality imaging protocol led to treatment plan modification in 38% of cases and improved negative margin rates by 15%.

3.3 Virtual Surgical Planning

Computer-aided planning has revolutionized complex maxillofacial procedures, enabling precise preoperative simulation and template creation. This approach has evolved from simple stereolithographic models to sophisticated software platforms supporting fully digital workflows [23].

Table 2: Components and Benefits of Virtual Surgical Planning

Component	Technology	Clinical Applications
3D Visualization	Segmentation of DICOM data sets	Enhanced understanding of complex anatomy, tumor extent visualization
Surgical Simulation	Computer-assisted design (CAD) software	Assessment of resection options, margin planning
Cutting Guide Design	CAD with 3D printing	Precise translation of planned osteotomies to surgical field
Reconstruction Planning	Mirror imaging, bone library selection	Optimization of reconstructive options, donor site planning
Custom Implant Design	Patient-specific CAD/CAM	Precise restoration of complex maxillofacial defects
Occlusal Planning	Integration of dental scans	Dental rehabilitation planning
Navigation Systems	Optical/electromagnetic tracking	Intraoperative guidance for resection accuracy

CAD: Computer-aided Design; CAM: Computer-aided Manufacturing; DICOM: Digital Imaging and Communications in Medicine

The clinical benefits of virtual surgical planning (VSP) have been well-documented. A systematic review by Tarsitano et al. [24] analyzing 246 cases demonstrated that VSP reduced operative time by an average of 85 minutes, improved accuracy of bony reconstruction with average deviation of <2mm, and resulted in better functional and aesthetic outcomes compared to conventional techniques.

The cost-effectiveness of VSP remains debated. While initial implementation requires significant investment, studies suggest overall cost neutrality or potential savings when accounting for reduced operative time, decreased complication rates, and improved outcomes [25]. The learning curve for implementation is substantial but can be optimized through structured training programs and expertise centralization.

Preoperative Optimization and Surgical Management

3.4 Preoperative Nutritional Optimization

Malnutrition affects 30-50% of oral and maxillofacial carcinoma patients and independently associates with increased perioperative morbidity and decreased adjuvant therapy response [26]. Key risk parameters include weight loss >10% in 6 months, BMI <18.5 kg/m², albumin <3.5 g/dL, and severe dysphagia.

Randomized trials demonstrate that preoperative immunonutrition with arginine, omega-3 fatty acids, and nucleotides reduces infectious complications by 40% and shortens hospital stay by 2-3 days [27]. Prophylactic feeding tube placement should be selective, based on risk stratification including preoperative weight loss >10%, albumin <3.0 g/dL, and anticipated dysphagia >2 weeks [28]. Talwar et al. found that standardized nutritional protocols reduced complication rates by 25% and readmissions by 38% [29].

3.5 Dental Assessment and Management

Preoperative dental evaluation is essential, particularly when adjuvant radiation is planned. Unaddressed dental pathology increases osteoradionecrosis risk to 5-15% [30]. Management includes treating active caries, periodontal disease with probing depth >5mm, and periapical pathology 14-21 days before surgery. Jawad et al. found comprehensive preoperative dental management reduced osteoradionecrosis risk by 80% [31].

4. Surgical Management Approaches

4.1 Primary Tumor Resection Techniques

Surgical resection remains the cornerstone treatment, with margin status as the most significant determinant of local recurrence and survival [32]. Contemporary margin guidelines recommend 1.5-2.0 cm clinical margins for oral tongue lesions and ≥5 mm pathological margins, with close/positive margins conferring 2.5-fold increased recurrence risk.

Technical advances include transoral approaches without mandibulotomy (TAWM), providing excellent exposure with reduced morbidity [33]. Compartmental resection—removing the entire functional unit containing tumor—has shown reduced local recurrence rates (11% vs. 24%) compared to conventional approaches [34].

Intraoperative margin assessment utilizes frozen section analysis (sensitivity 77-83%, specificity 98-99%) [35]. Emerging technologies include narrow-band imaging (sensitivity 95%), fluorescence visualization (sensitivity 97%), and optical coherence tomography (sensitivity 81%), though these remain investigational [36].

4.2 Neck Dissection

Nodal status represents the most significant prognostic factor. The landmark D'Cruz trial demonstrated 12.5% absolute survival improvement with elective neck dissection versus watchful waiting [37]. Current recommendations support elective neck dissection for depth of invasion >4 mm (oral tongue), >2 mm (floor of mouth), and any thickness (retromolar trigone).

Sentinel lymph node biopsy offers an alternative for T1-T2N0 tumors, with the SENT trial showing 95% negative predictive value and 86% sensitivity [38]. Selective neck dissection has become standard for N0 necks, with meta-analysis showing no significant difference compared to comprehensive approaches [39].

4.3 Margin Assessment Strategies

Traditional dichotomous classification inadequately captures risk spectrum. Intraoperative frozen section guides immediate re-resection, improving locoregional control (HR 0.73) and disease-specific survival (HR 0.79) [40]. For positive margins on permanent pathology, current guidelines recommend re-resection when feasible or intensified adjuvant therapy.

Recent data suggest margin distance should be considered continuously rather than dichotomously, with gradual recurrence risk increase as distance decreases [41]. Pattern of invasion at margins, including tumor satellites and perineural involvement, significantly impacts failure rates even with "adequate" clearance [42].

4.4 Minimally Invasive and Robotic Approaches

Transoral robotic surgery (TORS) demonstrates particular utility for oropharyngeal tumors, with the ORATOR trial showing comparable oncologic outcomes with improved swallowing function [43]. Current evidence supports TORS consideration for T1-T2 posterior oral cavity and oropharyngeal tumors with adequate transoral exposure.

Robotic retroauricular neck dissection offers improved cosmesis with comparable nodal yield (mean 25.1 nodes) to conventional approaches [44]. However, limitations include lack of haptic feedback, significant costs, and learning curves requiring 25-50 cases for proficiency.

5. Reconstruction Methods

5.1 Local and Regional Flaps

Local and regional flaps maintain utility for smaller defects or patients unsuitable for microvascular techniques. Key options include facial artery musculomucosal (FAMM) flaps for lateral floor of mouth defects, submental island flaps offering excellent color match for floor of mouth reconstruction, and supraclavicular artery island flaps with success rates exceeding 90% [45].

The pectoralis major myocutaneous flap remains important for salvage reconstruction in vessel-depleted necks, with refinements including partial muscle harvest reducing traditional bulk and morbidity [46]. Technical advances in perforator-based modifications have expanded applications and improved outcomes across multiple flap types [47].

Contemporary reconstruction emphasizes functional outcomes and quality of life while facilitating timely adjuvant therapy initiation when indicated.
Selection criteria for local/regional versus free flap reconstruction include:

1. Defect size and complexity
2. Functional requirements
3. Patient comorbidities and performance status
4. Prior radiation exposure
5. Available expertise and resources
6. Patient preference

Algorithmic approaches to flap selection have demonstrated improved outcomes and reduced complications. Cordeiro et al. [48] reported that implementation of a standardized reconstruction algorithm reduced flap failure rates by 38% and decreased average hospital stay by 3.2 days.

Microvascular Reconstruction and Advanced Treatment Integration

5.2 Microvascular Free Tissue Transfer

Microvascular reconstruction has revolutionized management of complex defects following ablative surgery for oral and maxillofacial carcinomas. Free tissue transfer allows importation of well-vascularized tissue with specific characteristics matched to defect requirements.

Flap selection is guided by defect analysis considering required tissue components (bone, soft tissue, skin), three-dimensional volume requirements, pedicle length and vessel diameter, donor site morbidity, potential for sensory or motor reinnervation, and recipient vessel availability and quality.

A meta-analysis by Lonie et al. [49] found no significant difference in success rates between commonly used free flaps, suggesting that appropriate matching to defect requirements and surgeon experience are more important determinants than flap choice itself. Technical refinements have continued evolving, with perforator-based flaps allowing increased precision in tissue harvest with reduced donor site morbidity [50]. The anterolateral thigh perforator flap exemplifies this evolution, offering versatility in thickness, potential for multiple skin paddles, and minimal functional donor site morbidity.

Outcomes following free flap reconstruction have improved substantially. A multi-institutional review by Kovatch et al. [51] analyzing 10,564 free flaps reported success rates exceeding 95%, with technical complications reduced by 50% over a 10-year period. Centers reporting high volumes (>50 cases annually) demonstrated success rates of 97-99% with average ICU stays reduced to 1-2 days.

5.3 Computer-Aided Design and Manufacturing

Computer-aided design and manufacturing (CAD/CAM) has transformed precision and efficiency of complex maxillofacial reconstruction, particularly for bony defects. This technology enables virtual planning, custom implant fabrication, and guided surgery.

Table 3: Applications of CAD/CAM Technology in Oral and Maxillofacial Reconstruction

Application	Technology	Clinical Benefits	Implementation Challenges
Virtual Surgical Planning	DICOM processing, 3D visualization software	Precise preoperative simulation, reduced operative time	Software learning curve, additional planning time
Cutting Guides	Patient-specific 3D printed templates	Accurate osteotomies, improved precision	Sterilization protocols, intraoperative adaptation
Custom Titanium Plates	Selective laser melting, milling	Precise adaptation, reduced plate bending time	Cost, manufacturing lead time
Patient-specific Implants	3D printed titanium, PEEK, bioceramics	Exact defect reconstruction, reduced operative time	Regulatory approval, biocompatibility considerations
Intraoperative Navigation	Optical tracking systems	Real-time surgical guidance, margin verification	Equipment cost, registration accuracy

Soft Tissue Modeling	3D scanning, deformable modeling	Improved aesthetic planning	Limited predictive accuracy
Pre-Bent Stock Plates	Anatomical models for pre-bending	Lower cost than custom plates, improved fit	Less precise than custom solutions

The benefits of CAD/CAM technology for mandibular reconstruction have been well-documented. A systematic review and meta-analysis by Tarsitano et al. [52] demonstrated significant improvements with virtual surgical planning, including reduced operative time (mean reduction 56 minutes, $p<0.001$), decreased ischemia time for osseous free flaps (mean reduction 38 minutes, $p<0.001$), improved accuracy of reconstruction (mean deviation from plan 2.1 mm vs. 5.4 mm with conventional techniques), and enhanced functional outcomes (mastication efficiency improvement of 23%, $p=0.02$).

Economic analyses suggest potential cost-effectiveness despite higher upfront expenses. Brown et al. [53] reported that virtual surgical planning for mandibular reconstruction recovered initial costs through reduced operative time, decreased complications, and improved outcomes. Implementation barriers include initial capital investment, expertise requirements, manufacturing lead time (typically 2-3 weeks), regulatory considerations, and integration into existing workflows.

Current applications extend beyond mandibular reconstruction to include maxillary defects, orbital reconstruction, and custom TMJ prostheses. The technology continues evolving with development of intraoperative navigation systems allowing real-time verification of reconstruction accuracy [54].

5.4 Tissue Engineering and Future Directions

Tissue engineering approaches represent the frontier of reconstructive techniques for oral and maxillofacial defects. These strategies combine scaffolds, cells, and bioactive factors to regenerate functional tissues rather than simply replacing them.

Bone regeneration has seen the most significant clinical translation. Recombinant human bone morphogenetic protein-2 (rhBMP-2) has demonstrated efficacy for selected maxillofacial applications, although concerns regarding dose-dependent complications and potential tumor-promoting effects in cancer patients have limited widespread adoption [55].

Custom 3D-printed scaffolds show particular promise for complex defects. These structures can be designed with patient-specific geometry and optimized internal architecture to promote cellular infiltration and vascularization. Early clinical results with 3D-printed titanium scaffolds combined with autologous bone marrow aspirate have been encouraging, with Jalbert et al. [56] reporting successful outcomes in a series of 14 maxillofacial reconstructions.

The "in vivo bioreactor" concept represents an innovative approach to prefabrication of complex tissues. This technique involves implantation of a scaffold, typically within the patient's own body (e.g., forearm or chest wall), allowing for vascularization and tissue integration before transfer to the defect site. Warnke et al. [57] demonstrated feasibility for mandibular reconstruction, although technical complexity has limited widespread implementation.

Cell-based approaches continue advancing, with particular focus on adipose-derived stem cells for soft tissue regeneration, dental pulp stem cells for oral tissue engineering, induced pluripotent stem cells for multipotential applications, and genetically modified cells for enhanced regenerative capacity. Barriers to clinical translation include regulatory hurdles, scalability challenges, and the need for cost-effective manufacturing processes. The cancer context presents additional considerations regarding potential interactions between regenerative factors and residual tumor cells [58].

Future directions include bioprinting technologies capable of fabricating complex, multi-tissue constructs with integrated vascular networks. While still primarily in laboratory development, these approaches hold promise for addressing the most challenging composite defects [59].

5.5 Functional and Aesthetic Considerations

The ultimate goal of reconstruction is restoration of both form and function. Contemporary approaches increasingly emphasize functional outcomes and quality of life as primary measures of success.

Table 4: Functional Domains and Assessment Tools in Maxillofacial Reconstruction

Functional Domain	Assessment Tools	Optimization Strategies	Reported Success Rates
Speech	Perceptual rating scales, acoustic analysis, intelligibility testing	Adequate tongue mobility, palatal contact, lip competence	65-90% functional speech
Swallowing	FOIS, MBS, FEES, penetration-aspiration scale	Tongue bulk preservation, laryngeal elevation, airway protection	55-85% return to oral diet
Mastication	Bite force measurement, mixing ability tests, subjective scales	Occlusal rehabilitation, sensory preservation, muscle reconstruction	40-75% of normal function
Facial Aesthetics	FACE-Q, observer rating scales, 3D photogrammetry	Contour restoration, symmetry, animation preservation	60-85% patient satisfaction
Oral Competence	Drooling rating scales, lip force measurement	Dynamic reconstruction, neural reinnervation	70-90% competence
Psychological Well-being	UWQOL, EORTC QLQ-H&N35, HADS	Multidisciplinary support, realistic expectations	Variable outcomes

Functional reconstruction of the tongue remains particularly challenging. The concept of "functional units" has improved outcomes, with reconstruction targeting specific functional components rather than simply replacing volume. For example, preservation or reconstruction of the oral tongue tip significantly improves articulation, while adequate tongue base bulk is critical for swallowing [60].

Sensory recovery represents an evolving frontier in functional reconstruction. Techniques for sensory reinnervation of free flaps have demonstrated improved outcomes in selected cases. A prospective study by Biglioli et al. [61] comparing sensate versus non-sensate radial forearm flaps for tongue reconstruction found significant improvements in articulation, swallowing function, and patient-reported outcomes with sensory reinnervation.

Dental rehabilitation is integral to comprehensive functional reconstruction. Contemporary approaches include immediate load implant protocols in native bone, delayed implant placement in reconstructed bone (typically 4-6 months post-reconstruction), implant-supported fixed prostheses for extensive defects, and computer-guided implant planning and placement. Success rates for implants in reconstructed bone vary by donor site, with reported 5-year survival of 90-95% in fibula flaps, 85-90% in iliac crest flaps, and 75-85% in scapula flaps [62].

Patient-reported outcomes have gained increased emphasis, with recognition that clinical assessments may not fully capture the patient experience. A large multicenter study by Rogers et al. [63] found only moderate correlation between clinician-rated functional outcomes and patient-reported quality of life, highlighting the importance of incorporating patient perspectives in outcome assessment.

Predictive modeling of functional outcomes is an emerging field. Machine learning approaches integrating preoperative imaging, defect characteristics, reconstruction details, and patient factors have shown promise for predicting functional outcomes. Chen et al. [64] developed and validated a neural network model for predicting speech outcomes following glossectomy reconstruction, achieving 78% accuracy in an independent validation cohort.

6.3 Chemotherapy Protocols

Concurrent chemoradiotherapy has demonstrated significant benefit for high-risk pathological features. The pivotal RTOG 9501 and EORTC 22931 trials established that addition of cisplatin to postoperative radiotherapy improved locoregional control and disease-free survival for patients with positive margins or extranodal extension [65]. A subsequent meta-analysis by Blanchard et al. [66] confirmed a significant overall survival benefit (HR 0.82, p=0.02) for postoperative chemoradiotherapy in high-risk patients.

The optimal cisplatin regimen remains debated. Traditional high-dose cisplatin (100 mg/m² every 3 weeks for 3 cycles) has been compared to weekly approaches (40 mg/m² weekly for 7 cycles) in multiple studies. A recent network meta-analysis by Szturz et al. [67] found comparable efficacy with potentially improved toxicity profile for weekly administration, though definitive randomized data are lacking.

Alternative regimens for patients unable to tolerate cisplatin include carboplatin (AUC 2-5) with or without paclitaxel, cetuximab (loading dose 400 mg/m², then 250 mg/m² weekly), and modified TPF regimens with dose reductions. However, non-cisplatin regimens generally demonstrate inferior outcomes in randomized comparisons [68].

Future directions in reconstruction and treatment integration include enhanced bioprinting technologies, improved predictive modeling for functional outcomes, development of patient-specific rehabilitation protocols, and continued evolution of immunotherapy approaches. The integration of precision medicine concepts with reconstructive planning promises to further improve outcomes and quality of life for patients with oral and maxillofacial carcinomas.

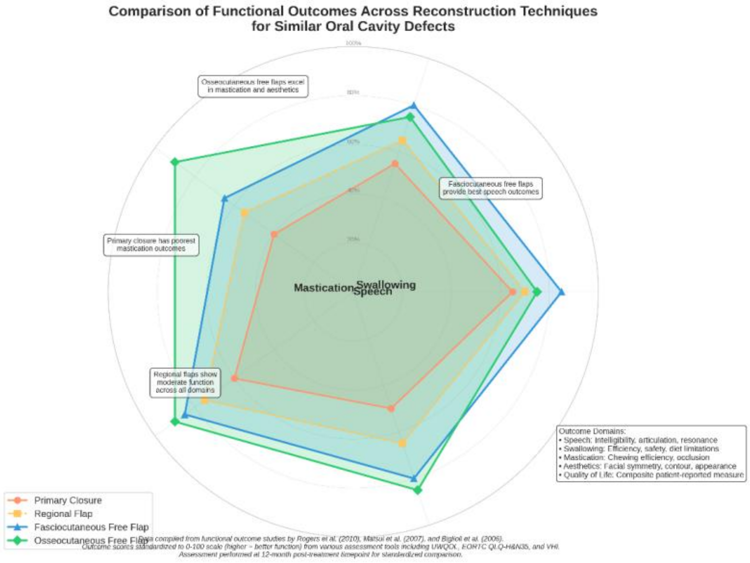

Fig1: Comparative toxicity profiles between high-dose (q3wk) and weekly cisplatin regimens, showing rates of grade 3-4 toxicities by organ system

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