

Review

Perioperative, Surgery-Anchored Multimodal Sequencing for Locally Advanced Oral Cavity Squamous Cell Carcinoma: State of the Art and Future Directions

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Abstract

Surgery remains the cornerstone for resectable, locally advanced oral cavity squamous cell carcinoma. Optimal outcomes rely on precise patient selection, oncologic extirpation with pathologic risk stratification, timely adjuvant radiotherapy with or without concurrent systemic therapy, evidence-based reconstructive strategies, and more recently well-designed neoadjuvant/adjuvant immunotherapy.

We synthesized Level I–III evidence and contemporary consensus from high-impact journals and guidelines on: staging refinements, margin/depth of invasion standards, elective neck management, timing/technique of post-operative radiotherapy/post-operative concurrent chemoradiotherapy reconstruction and enhanced recovery after surgery, and perioperative systemic therapy.

Landmark randomized trials established that in high-risk postoperative cohorts (positive margin and/or extranodal extension), adding high-dose cisplatin to post-operative radiotherapy improves locoregional control and disease-free survival; weekly cisplatin (40 mg/m²) is non-inferior to 3-weekly 100 mg/m² and is less toxic. Elective management of the cN0 neck improves survival versus therapeutic neck dissection after nodal relapse, and sentinel node biopsy is oncologically equivalent to selective neck dissection in cT1–2N0 disease with lower early morbidity. Intensity-modulated radiation therapy based post-operative radiotherapy reduces xerostomia versus 3D-CRT; delays beyond ~6 weeks after surgery and prolonged treatment package time are associated with worse survival. Early signals support perioperative anti-PD-1 therapy in resectable head and neck squamous cell carcinoma, while adjuvant anti-PD-L1 monotherapy after standard of care was negative. Reconstruction tailored to defect class prioritizing function and adjuvant readiness achieves high flap survival, enhanced recovery after surgery pathways shorten length of stay without compromising safety.

A surgery-anchored, time-sensitive, risk-adapted sequence incorporating modern neck management, intensity-modulated radiation therapy based post-operative radiotherapy/post-operative concurrent chemoradiotherapy reconstruction, and selective immunotherapy yields the best current outcomes for advanced oral cavity

squamous cell carcinoma. Ongoing trials will define perioperative immunotherapy integration, de-escalation for intermediate risk, and biomarkers refining indications.

Keywords: oral cavity squamous cell carcinoma, surgery, neck dissection, depth of invasion, postoperative radiotherapy.

1. Introduction

Oral cavity cancers account for a substantial proportion of head and neck squamous cell carcinomas (HNSCC) and impose a significant global burden on survival, function, and quality of life. Unlike oropharyngeal disease—where HPV biology drives a distinct natural history – oral cavity squamous cell carcinoma (OCSCC) is largely HPV negative and classically associated with tobacco, alcohol, and, in certain regions, areca nut/smokeless tobacco exposure. Patients frequently present with advanced primary tumor size (T3–T4) and/or nodal involvement, with a considerable subset harboring aggressive pathological features such as perineural invasion (PNI), lymphovascular invasion (LVI), the most aggressive worst pattern of invasion (WPOI), and extranodal extension (ENE) [1].

In this setting, surgery offers the highest probability of achieving durable local control through en bloc removal of the primary tumor and appropriate management of the neck. However, the biology of advanced OCSCC with significant risks of occult cervical metastases, peritumoral spread along mucosal and fascial planes, and propensity for locoregional failure necessitates a surgery anchored yet deliberately sequenced multimodal approach. During the past

decade, several developments have converged to enable more refined care pathways: (i) staging refinements in AJCC 8th edition, incorporating depth of invasion (DOI) and extranodal extension (ENE), which improve prognostic stratification over the 7th edition; (ii) technical maturation of radiotherapy, particularly intensity modulated radiotherapy (IMRT) with organ at risk sparing that reduces long term xerostomia and dysphagia; (iii) standardization of perioperative care via enhanced recovery after surgery (ERAS) bundles, which lead to shorter hospital stays and fewer complications in head and neck free flap surgery; and (iv) evolution of systemic therapy, including high level evidence supporting concurrent cisplatin with postoperative radiotherapy in high risk patients [2-5].

This review synthesizes contemporary evidence to provide a practical, academically rigorous framework for clinicians planning surgery anchored, time sensitive multimodal therapy for advanced OCSCC. We emphasize indications, timing, and integration across modalities; highlight areas of consensus versus controversy; and offer implementable clinical pathways.

2. Methodology

We undertook a targeted narrative review focusing on randomized controlled trials (RCTs), pivotal prospective or large high-quality retrospective cohorts, and authoritative consensus/guideline documents published predominantly between 2011 and 2025. Databases queried included PubMed, Web of Science, and Google Scholar. We prioritized high-impact sources (e.g., NEJM, Lancet Oncology, JCO, IJROBP, Oral Oncology, Head & Neck), while incorporating seminal earlier trials that established current standards.

Inclusion and prioritization

Eligible evidence addressed at least one of the following domains: (1) staging and risk stratification for OCSCC, especially DOI and ENE; (2) surgical margins, intraoperative margin assessment and neck management (elective neck dissection (END) vs sentinel node biopsy (SNB)); (3) adjuvant radiotherapy (PORT) or chemoradiotherapy (POCRT) indications, dose, technique, and timing; (4) systemic therapy schedules

(weekly vs q3-weekly cisplatin) in the postoperative setting; (5) perioperative immunotherapy; (6) reconstructive strategies and ERAS protocols; and (7) survivorship and functional outcomes.

Quality considerations

Randomized evidence was weighted highest. For nonrandomized studies, we favored multi-institutional cohorts with clear inclusion criteria, standardized outcome definitions e.g., locoregional control (LRC), disease-free survival (DFS), event-free survival (EFS), overall survival (OS), and adequate adjustment for confounders e.g., stage, margin status. Where evidence was heterogeneous, we present consensus-oriented recommendations and explicitly acknowledge uncertainty.

3. Staging refinements that drive sequencing

DOI and ENE in AJCC 8th edition

The American Joint Committee on Cancer (AJCC) 8th edition incorporated DOI into T classification and codified ENE within N staging for oral cavity cancers, changes that better reflect biologic aggressiveness and improve prognostic stratification [6]. DOI correlates with both the risk of occult nodal metastasis and local failure, whereas ENE is among the strongest adverse prognosticators in OCSCC cohorts [6-8]. Practically, DOI reframes management of the clinically node-negative (cN0) neck—supporting END/SNB when invasion extends beyond superficial thresholds and ENE after pathologic evaluation adjudicates patients to a high-risk postoperative category warranting concurrent chemotherapy with PORT [6,9,10].

Measurement nuances and reproducibility

Accurate DOI quantification requires careful orientation of the specimen and correct identification of the reconstructed mucosal surface; interobserver variability is non-trivial and can shift pT stage assignment in a meaningful fraction of cases, underscoring the need for standardized grossing, inking, and histologic measurement protocols [7]. ENE reporting should distinguish microscopic versus macroscopic ENE and record extent of extranodal

spread and nodal burden, as these features modulate risk even within ENE-positive disease [6,8].

Beyond AJCC: complementary risk markers

While DOI and ENE anchor contemporary staging, additional markers enrich risk stratification. Worst pattern of invasion (WPOI-5; e.g., satellite tumor islands and extratumoral PNI/LVI) has shown independent adverse prognostic associations in early-stage OCSCC [9]. Lymph node ratio (positive/harvested) also carries strong prognostic signal for recurrence and survival, complementing absolute nodal counts [11]. Treating margin distance as a continuous variable and integrating perineural/LVI and high DOI into multivariable models can refine indications for PORT versus POCRT and inform discussions on de-intensification or intensification [6,9,11].

Implications. (i) DOI ≥ 4 mm typically justifies END or SNB even in cN0 disease; (ii) any ENE elevates postoperative risk sufficiently to mandate POCRT barring contraindications; (iii) intermediate-risk features (close margins, multiple nodes without ENE, PNI/LVI, high DOI) favor PORT with meticulous target delineation [6,8, 9-11].

4. Surgical principles: margins, primary control, and neck management

Margins and DOI

Oncologic margins remain the single most powerful modifiable determinant of local control. The historical binary of “clear ≥ 5 mm” versus “close < 5 mm” is a helpful heuristic but may oversimplify the biologic continuum. Deep soft-tissue and muscular planes, periosteum, and neurovascular bundles often represent the true high-risk interfaces in oral cavity surgery [12-14]. Intraoperative frozen sections can guide re-resection, yet sensitivity varies by sampling method. A programmatic approach—three-dimensional mapping of margin sites, standardized communication between surgeon and pathologist, and readiness to perform targeted re-excisions—improves R0 rates without undue morbidity [14-16]. Mandibular involvement requires tailored strategy: marginal mandibulectomy may suffice for superficial cortical erosion with preserved medullary integrity, whereas segmental resection is indicated for medullary invasion or pathologic fracture risk. Decisions should be preplanned with reconstructive options to avoid compromise of postoperative radiation planning [17-18].

Elective management of the cN0 neck

Randomized data support END at the time of primary surgery for early oral cavity cancers, improving OS and DFS versus observation with delayed therapeutic neck dissection [19-20]. Where expertise and validation pathways exist, SNB provides oncologic equivalence with lower early morbidity and faster recovery [21]. Selection between END and SNB should consider tumor subsite, DOI, imaging quality, lymphoscintigraphy reliability, and institutional experience [19-21, 23]. Regardless of strategy, timely final pathology and expedited referral to radiation oncology are critical to meet PORT timing benchmarks.

Extent and levels

Selective neck dissection typically encompasses levels I–III for many oral cavity subsites; level IV is commonly added for tongue/floor-of-mouth primaries with deeper DOI or suspicious imaging.

Level IIb preservation is feasible absent radiologic concern. Midline or near-midline lesions warrant bilateral evaluation to avoid contralateral failure.

5. Reconstruction that enables function and adjuvant readiness

Principles and defect-oriented selection

Reconstruction must reconcile oncologic safety, functional restoration, and adjuvant readiness. Defect classifications (e.g., Brown for mandibular continuity defects; Urken for composite oromandibular defects) help map flap choice [25].

Soft tissue: The radial forearm free flap (RFFF) provides thin, pliable tissue suited for tongue and floor-of-mouth defects requiring precision in articulation [26]; the anterolateral thigh (ALT) flap offers reliable volume with lower donor morbidity and can be thinned [27]. The medial sural artery perforator (MSAP) flap is an increasingly popular option for hemiglossectomy due to its favorable thickness profile [28].

Bony reconstruction: Fibula free flap remains the workhorse for segmental mandibular defects, offering long bone stock and the possibility of virtual surgical planning (VSP) for accurate osteotomy and plate fit [29]. Scapular or iliac crest options provide alternatives in select anatomies or when multiple contour curves are desired [30].

Adjuvant readiness should influence flap design: avoid bulky insets that obscure the oral cavity during simulation or compromise IMRT dosimetry; anticipate percutaneous endoscopic gastrostomy (PEG)

Dissection yield should be adequate to support accurate pathologic staging (often ≥ 18 nodes in total), enabling appropriate adjuvant decisions [23–24].

dependence and strive for early oral intake when safe [31].

Functional outcomes and rehabilitation

Speech and swallowing outcomes hinge on tongue mobility/volume, mucosal pliability, dentition/occlusion, and timely rehabilitation [32]. Multidisciplinary input (speech-language pathology, nutrition, dental oncology) beginning preoperatively fosters realistic expectations and adherence. Early trismus prevention (jaw mobilization, tongue range-of-motion exercises) and lymphedema therapy mitigate late dysfunction [33].

ERAS pathways

ERAS bundles tailored to head and neck free-flap surgery include: prehabilitation and nutrition optimization, carbohydrate loading when appropriate, meticulous airway planning, multimodal analgesia with opioid-sparing strategies, judicious fluids, standardized thromboprophylaxis, and early mobilization [34]. Evidence shows reduced length of stay and no increase in complications when ERAS is faithfully implemented. Early oral feeding following mucosal free-flap reconstruction is increasingly supported when flap perfusion is stable and there is no anastomotic concern [35].

6. Adjuvant radiotherapy (PORT) and chemoradiotherapy (POCRT)

Indications

High-risk postoperative features—principally positive (involved) margins and/or ENE—warrant concurrent cisplatin with PORT (POCRT) given the demonstrated gains in LRC and survival [36–39]. Intermediate-risk features—including pT3–4 disease, multiple nodes without ENE, close margins, PNI/LVI, high DOI, adverse WPOI—typically merit PORT alone; patient comorbidity, renal function, and hearing status influence the feasibility of concurrent cisplatin.

Dose, volumes and technique

Standard PORT prescription is 60–66 Gy in 2.0 Gy fractions, with dose painting to high-risk tumor bed and involved nodal basins, and elective coverage (e.g., 54–56 Gy) to at-risk neck levels. IMRT/volumetric modulated arc therapy (VMAT) with parotid/submandibular sparing is preferred to reduce

xerostomia [1]. Contemporary atlases provide structured guidance on clinical target volumes (e.g., tumor bed; involved nodal levels; elective nodal levels) with attention to mucosal margins, periosteal surfaces, neurovascular pathways, and surgical clip placement [40–43]. Organ-at-risk constraints commonly include mean parotid dose < 26 Gy when achievable, contralateral submandibular sparing, oral cavity mucosa moderation to limit mucositis, and laryngeal/esophageal reduction in swallow-sparing plans; mandibular dose moderation is critical to reduce ORN risk and should be coordinated with pre-RT dental clearance [42].

Timing and treatment package time (TPT)

Time to PORT initiation should be ≤ 6 weeks post-surgery whenever feasible. Delays beyond this window and prolonged TPT (surgery to last fraction) are associated with inferior outcomes, likely reflecting tumor repopulation and missed windows for micrometastatic eradication [40]. Institutions should implement fast-track pathways: rapid pathology turnaround, early dental oncology consults, simulation slots reserved for postoperative cases, and proactive social support to ensure adherence.

Concurrent cisplatin schedule and supportive care

The historical standard is q3-weekly cisplatin 100 mg/m² on days 1, 22, and 43 [37,38]. Robust contemporary randomized evidence supports weekly cisplatin 40 mg/m² as non-inferior for OS in the postoperative high-risk setting, with improved

tolerability (less nephro/oto-toxicity and hematologic toxicity) [41]. Dosing choice should be individualized based on patient frailty, renal reserve, audiometric baseline, and logistics. Supportive care is integral: guideline-concordant antiemesis (NK1/5-HT3/dexamethasone for highly emetogenic risk), hydration with magnesium supplementation, nephroprotection, and audiology monitoring; early nutrition intervention (dietitian co-management; selective PEG) and prophylactic swallowing therapy reduce acute weight loss and late dysphagia. For cisplatin-ineligible patients, alternative radiosensitizers (e.g., cetuximab) have not consistently matched cisplatin outcomes and are generally reserved for specific contraindications or clinical trials (see also practice guidelines cited earlier).

7. Perioperative systemic therapy beyond cisplatin

Induction chemotherapy

For technically unresectable or borderline-resectable OCSCT, TPF-based induction can downstage disease to permit curative resection in selected patients [44,45]. This approach requires careful selection (performance status, organ function), close toxicity monitoring (myelosuppression, mucositis, neuropathy), and crisp coordination so as not to compromise definitive local therapy. Prospective data support improved resectability; however, routine use outside of these scenarios is not indicated.

Immunotherapy in the resectable setting

Perioperative anti-PD-1 strategies (neoadjuvant plus adjuvant) have demonstrated event-free survival improvements in resectable HNSCC without reducing surgical completion rates in trial contexts (KEYNOTE-689) [46]. Signal magnitude appears greater in HPV-negative disease and in patients with PD-L1-positive tumors, though definitive biomarker thresholds for oral cavity-specific practice remain under active study. Key practical considerations include:

- Surgical timing: Neoadjuvant therapy must not delay extirpation beyond acceptable windows;

multidisciplinary team (MDT) coordination and rapid-access operating room scheduling are essential.

- Wound healing and immune-related AEs (irAEs): Most irAEs are manageable; vigilance for endocrinopathies (thyroiditis, adrenal insufficiency) is important given baseline post-RT hypothyroidism risk.
- Integration with PORT/POCRT: Overlapping toxicities (dermatologic, mucosal) necessitate careful sequencing and supportive care.

In contrast, adjuvant anti-PD-L1 monotherapy after standard local therapy did not improve EFS/OS in high-risk cohorts (IMvoker010) [47], underscoring that simply extending adjuvant systemic therapy without biological selection may be insufficient.

Lessons from the recurrent/metastatic setting

First-line pembrolizumab (alone for PD-L1-expressing tumors or combined with platinum/5-FU) and nivolumab after platinum failure improved OS and patient-reported outcomes (KEYNOTE-048 & CheckMate-141) [48–50]. While these data derive from R/M populations, they offer mechanistic support for perioperative immunotherapy and inform salvage strategies if postoperative recurrence occurs.

8. Practical sequencing pathways

Upfront resectable, high-risk on final pathology (positive margin and/or ENE)

- Step 1: En bloc resection of the primary with appropriate neck dissection (END/SND) and immediate reconstruction.
- Step 2: Expedited dental optimization and IMRT simulation within 1 week; PEG considered selectively.

- Step 3: POCRT to 60–66 Gy with either q3-weekly or weekly cisplatin, initiated ≤ 6 weeks post-op [37–41].

- Step 4: Early, proactive swallowing therapy and lymphedema management; monitor for nephro-/ototoxicity and cytopenias.

Upfront resectable, intermediate risk

- Step 1: Resection + END/SNB as indicated by DOI and subsite.

- Step 2: PORT 60–63 Gy (risk-adapted volumes) ≤6 weeks; no concurrent chemotherapy [40, 43].

- Step 3: Standardized survivorship plan with dental and speech-language follow-up.

Borderline/technically unresectable disease

- Option A: Induction TPF aiming for conversion to R0 resection, followed by risk-adapted PORT/POCRT [44, 45].

- Option B: Primary CRT where resection remains unfeasible; consider clinical trial enrollment and early palliative/supportive care integration.

Perioperative immunotherapy candidate

MDT evaluation for neoadjuvant anti-PD-1, ensuring surgical slots are secured in advance and PORT planning proceeds in parallel [46].

Vigilant toxicity monitoring and coordinated transitions between surgery, radiation, and adjuvant immunotherapy.

Managing positive or close margins after final pathology

Re-resection should be pursued when anatomically feasible and functionally reasonable.

If re-resection is not possible, POCRT with boosted tumor bed dosing is indicated; reconstructive modifications (e.g., debulking) may be necessary to optimize dosimetry [37–39, 43].

9. Survivorship and toxicity mitigation

Acute toxicities and their prevention

Mucositis, odynophagia, dermatitis, dysgeusia, xerostomia, and weight loss are common during PORT/POCRT. Prophylactic oral care protocols, early nutrition support, and swallow therapy mitigate severity. Randomized trials confirm prophylactic swallowing exercises reduce dysphagia severity [51]. Pain management should follow multimodal principles with careful opioid stewardship.

Late effects and monitoring

Xerostomia and dysphagia: IMRT reduces severity but does not eliminate risk; DARS trial confirmed benefit of dysphagia-optimized IMRT [52].

Hypothyroidism: Neck irradiation predisposes to thyroid dysfunction; check TSH at 6–12 months and annually thereafter [53,54].

Osteoradionecrosis (ORN): Pre-RT dental optimization, conservative extractions, and mandibular dose moderation reduce risk; staged protocols manage established ORN [55–57,58].

Lymphedema and fibrosis: Early referral for decongestive therapy and jaw-stretching regimens helps preserve range of motion.

Hearing loss and neuropathy: Baseline and interval audiometry for cisplatin counsel regarding tinnitus and balance issues [55, 59–61].

Psychosocial and functional rehabilitation

Speech intelligibility, return to work, body image, and social reintegration are central outcomes. Access to dental prosthodontics, cessation programs, and mental health support should be integrated. Patient-reported outcomes (MDADI, UW-QOL) guide structured interventions [56,62].

Follow-up schedule

A pragmatic schedule includes visits every 1–3 months in year 1, every 2–4 months in year 2, every 4–6 months in years 3–5, and annually thereafter, with imaging directed by symptoms, exam findings, and risk profile. Dental and thyroid follow-up are embedded at defined intervals [53,54,57,58].

10. Future directions

Several avenues are poised to reshape sequencing in advanced OCSCC:

Biomarker-refined perioperative immunotherapy: Integration of PD-L1 (CPS), immune gene signatures, and circulating tumor DNA (ctDNA)/molecular residual disease (MRD) assays may select patients most likely to benefit from neoadjuvant/adjuvant immune strategies [46,63–66]. De-escalation for intermediate risk: Trials exploring PORT dose reduction or omission of elective volumes in carefully profiled patients could

lower toxicity while preserving control [43]. Adaptive and automated radiotherapy: On-treatment anatomical changes can be addressed with adaptive replanning; AI-based auto-contouring and QA may shorten timelines and standardize care [67–69]. Function-preserving reconstruction: Prospective comparisons of RFFF/ALT/MSAP with standardized speech/swallow endpoints will inform flap choice [33]. Implementation science and equity: Reducing delays to PORT, ensuring access to IMRT and multidisciplinary rehabilitation,

and addressing social determinants will yield survival gains comparable to pharmacologic advances [40]. Pragmatic trials and real-world evidence: Embedding registries and learning-health-system designs will accelerate translation of perioperative immunotherapy and ERAS innovations into routine practice while safeguarding safety and value.

Conflict of interests. The authors declare no conflicts of interest.

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References

1. Heusch, G., & Schulz, R. (2011). A radical view on the contractile machinery in human heart failure. *Journal of the American College of Cardiology*, 57(3), 310–312. <https://doi.org/10.1016/j.jacc.2010.06.057>
2. Garrel, R., Poissonnet, G., Moyà Plana, A., Fakhry, N., Dolivet, G., Lallemand, B., Sarini, J., Vergez, S., Guelfucci, B., Choussy, O., Bastit, V., Richard, F., Costes, V., Landais, P., Perriard, F., Daures, J. P., de Verbizier, D., Favier, V., & de Boutray, M. (2020). Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 38(34), 4010–4018. <https://doi.org/10.1200/JCO.20.01661>
3. Fasunla, A. J., Greene, B. H., Timmesfeld, N., Wiegand, S., Werner, J. A., & Sesterhenn, A. M. (2011). A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. *Oral oncology*, 47(5), 320–324. <https://doi.org/10.1016/j.oraloncology.2011.03.009>
4. Bernier, J., Dometge, C., Ozsahin, M., Matuszewska, K., Lefèbvre, J. L., Greiner, R. H., Giralt, J., Maingon, P., Rolland, F., Bolla, M., Cognetti, F., Bourhis, J., Kirkpatrick, A., van Glabbeke, M., & European Organization for Research and Treatment of Cancer Trial 22931 (2004). Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *The New England journal of medicine*, 350(19), 1945–1952. <https://doi.org/10.1056/NEJMoa032641>
5. Cooper, J. S., Pajak, T. F., Forastiere, A. A., Jacobs, J., Campbell, B. H., Saxman, S. B., Kish, J. A., Kim, H. E., Cmelak, A. J., Rotman, M., Machtay, M., Ensley, J. F., Chao, K. S., Schultz, C. J., Lee, N., Fu, K. K., & Radiation Therapy Oncology Group 9501/Intergroup (2004). Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *The New England journal of medicine*, 350(19), 1937–1944. <https://doi.org/10.1056/NEJMoa032646>
6. Ghantous, Y., Nashef, A., Sidransky, D., Abdelraziq, M., Alkeesh, K., Araidy, S., Koch, W., Brait, M., & Abu El-Naaj, I. (2022). Clinical and Prognostic Significance of the Eighth Edition Oral Cancer Staging System. *Cancers*, 14(19), 4632. <https://doi.org/10.3390/cancers14194632>
7. Allen-Proctor, M. K., Rahman, M., Reddy, C. A., Koyfman, S. A., Chute, D. J., & Griffith, C. C. (2022). Variability in Depth of Invasion Measurements in Carcinomas of the Oral Cavity and the Effect on Pathologic Tumor Staging. *Head and neck pathology*, 16(4), 963–968. <https://doi.org/10.1007/s12105-022-01439-4>
8. Wreesmann, V. B., Katabi, N., Palmer, F. L., Montero, P. H., Migliacci, J. C., Gönen, M., Carlson, D., Ganly, I., Shah, J. P., Ghossein, R., & Patel, S. G. (2016). Influence of extracapsular nodal spread extent on prognosis of oral squamous cell carcinoma. *Head & neck*, 38 Suppl 1(Suppl 1), E1192–E1199. <https://doi.org/10.1002/hed.24190>
9. Mohamed, S., Jawad, H., Sullivan, R. O., Callanan, D., Sheahan, P., & Feeley, L. (2023). Significance of Worst Pattern of Invasion-5 in Early-Stage Oral Cavity Squamous Cell Carcinoma. *Head and neck pathology*, 17(3), 679–687. <https://doi.org/10.1007/s12105-023-01571-9>
10. Aaboubout, Y., van der Toom, Q. M., de Ridder, M. A., De Herdt, M. J., van der Steen, B., van Lanschot, C. G., ... & Koljenović, S. (2021). Is the depth of invasion a marker for elective neck dissection in early oral squamous cell carcinoma?. *Frontiers in Oncology*, 11, 628320. <https://doi.org/10.3389/fonc.2021.628320>

11. Ding, D., Stokes, W., Eguchi, M., Hararah, M., Sumner, W., Amini, A., Goddard, J., Somerset, H., Bradley, C., McDermott, J., Raben, D., & Karam, S. D. (2019). Association Between Lymph Node Ratio and Recurrence and Survival Outcomes in Patients With Oral Cavity Cancer. *JAMA otolaryngology-- head & neck surgery*, 145(1), 53–61. <https://doi.org/10.1001/jamaoto.2018.2974>
12. Zandoni, D. K., Migliacci, J. C., Xu, B., Katabi, N., Montero, P. H., Ganly, I., Shah, J. P., Wong, R. J., Ghossein, R. A., & Patel, S. G. (2017). A Proposal to Redefine Close Surgical Margins in Squamous Cell Carcinoma of the Oral Tongue. *JAMA otolaryngology-- head & neck surgery*, 143(6), 555–560. <https://doi.org/10.1001/jamaoto.2016.4238>
13. Tasche, K. K., Buchakjian, M. R., Pagedar, N. A., & Sperry, S. M. (2017). Definition of "Close Margin" in Oral Cancer Surgery and Association of Margin Distance With Local Recurrence Rate. *JAMA otolaryngology-- head & neck surgery*, 143(12), 1166–1172. <https://doi.org/10.1001/jamaoto.2017.0548>
14. Long, S. M., Mclean, T., Valero Mayor, C., Fitzgerald, C. W. R., Feit, N. Z., Katabi, N., Xu, B., Cohen, M. A., Ganly, I., Ghossein, R. A., & Patel, S. G. (2022). Use of Intraoperative Frozen Section to Assess Final Tumor Margin Status in Patients Undergoing Surgery for Oral Cavity Squamous Cell Carcinoma. *JAMA otolaryngology-- head & neck surgery*, 148(10), 911–917. <https://doi.org/10.1001/jamaoto.2022.2131>
15. Gur, A., Soffer, M., Blanck, P. D., Quinn, G., & Rimmerman, A. (2023). Pre- and Post-COVID-19 Outcomes for Israelis With Intellectual and Developmental Disabilities in the Community. *Intellectual and developmental disabilities*, 61(6), 454–467. <https://doi.org/10.1352/1934-9556-61.6.454>
16. Sunkara, P. R., Graff, J. T., & Cramer, J. D. (2023). Association of Surgical Margin Distance With Survival in Patients With Resected Head and Neck Squamous Cell Carcinoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery*, 149(4), 317–326. <https://doi.org/10.1001/jamaoto.2022.5186>
17. Li, C., Guo, Z., Wang, H., & others. (2017). Medullary vs cortical mandibular invasion affects prognosis in oral SCC. *Journal of Oral and Maxillofacial Surgery*, 75(7), 1477–1490. <https://doi.org/10.1016/j.joms.2016.08.005>
18. Chiesa-Estomba, C. M., Mayo-Yanez, M., Manelli, G., Molteni, G., Lechien, J., Fakhry, N., Melkane, A., Calvo-Henriquez, C., Kalfert, D., & Ayad, T. (2023). Marginal versus Segmental Mandibulectomy in the Treatment of Oral Cavity Cancer: A Systematic Review and Meta-analysis. *International archives of otorhinolaryngology*, 27(4), e733–e743. <https://doi.org/10.1055/s-0042-1750764>
19. D'Cruz, A. K., Vaish, R., Kapre, N., Dandekar, M., Gupta, S., Hawaldar, R., Agarwal, J. P., Pantvaidya, G., Chaukar, D., Deshmukh, A., Kane, S., Arya, S., Ghosh-Laskar, S., Chaturvedi, P., Pai, P., Nair, S., Nair, D., Badwe, R., & Head and Neck Disease Management Group (2015). Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *The New England journal of medicine*, 373(6), 521–529. <https://doi.org/10.1056/NEJMoa1506007>
20. Hutchison, I. L., Ridout, F., Cheung, S. M. Y., Shah, N., Hardee, P., Surwald, C., Thiruchelvam, J., Cheng, L., Mellor, T. K., Brennan, P. A., Baldwin, A. J., Shaw, R. J., Halfpenny, W., Danford, M., Whitley, S., Smith, G., Bailey, M. W., Woodward, B., Patel, M., McManners, J., ... Hackshaw, A. (2019). Nationwide randomised trial evaluating elective neck dissection for early stage oral cancer (SEND study) with meta-analysis and concurrent real-world cohort. *British journal of cancer*, 121(10), 827–836. <https://doi.org/10.1038/s41416-019-0587-2>
21. Garrel, R., Poissonnet, G., Moyà Plana, A., Fakhry, N., Dolivet, G., Lallemand, B., Sarini, J., Vergez, S., Guelfucci, B., Choussy, O., Bastit, V., Richard, F., Costes, V., Landais, P., Perriard, F., Daurès, J. P., de Verbizier, D., Favier, V., & de Boutray, M. (2020). Equivalence Randomized Trial to Compare Treatment on the Basis of Sentinel Node Biopsy Versus Neck Node Dissection in Operable T1-T2N0 Oral and Oropharyngeal Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 38(34), 4010–4018. <https://doi.org/10.1200/JCO.20.01661>
22. Robbins, K. T., Shaha, A. R., Medina, J. E., Califano, J. A., Wolf, G. T., Ferlito, A., Som, P. M., Day, T. A., & Committee for Neck Dissection Classification, American Head and Neck Society (2008). Consensus statement on the classification and terminology of neck dissection. *Archives of otolaryngology--head & neck surgery*, 134(5), 536–538. <https://doi.org/10.1001/archotol.134.5.536>
23. Koyfman, S. A., Ismaila, N., Crook, D., D'Cruz, A., Rodriguez, C. P., Sher, D. J., Silbermins, D., Sturgis, E. M., Tsue, T. T., Weiss, J., Yom, S. S., & Holsinger, F. C. (2019). Management of the Neck in Squamous Cell Carcinoma

of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, 37(20), 1753–1774. <https://doi.org/10.1200/JCO.18.01921>

24. Ebrahimi, A., Clark, J. R., Amit, M., Yen, T. C., Liao, C. T., Kowalski, L. P., Kreppel, M., Cernea, C. R., Bachar, G., Villaret, A. B., Fliss, D., Fridman, E., Robbins, K. T., Shah, J. P., Patel, S. G., & Gil, Z. (2014). Minimum nodal yield in oral squamous cell carcinoma: defining the standard of care in a multicenter international pooled validation study. *Annals of surgical oncology*, 21(9), 3049–3055. <https://doi.org/10.1245/s10434-014-3702-x>

25. Brown, J. S., Rogers, S. N., McNally, D. N., & Boyle, M. (2000). A modified classification for the maxillectomy defect. *Head & neck*, 22(1), 17–26. [https://doi.org/10.1002/\(sici\)1097-0347\(200001\)22:1<17::aid-hed4>3.0.co;2-2](https://doi.org/10.1002/(sici)1097-0347(200001)22:1<17::aid-hed4>3.0.co;2-2)

26. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 16-1989. A 36-year-old man with peripheral vascular disease. (1989). *The New England journal of medicine*, 320(16), 1068–1076. <https://doi.org/10.1056/NEJM198904203201608>

27. Doi, K., Kuwata, N., Kawakami, F., Hattori, Y., Otsuka, K., & Ihara, K. (1999). Limb-sparing surgery with reinnervated free-muscle transfer following radical excision of soft-tissue sarcoma in the extremity. *Plastic and reconstructive surgery*, 104(6), 1679–1687. <https://doi.org/10.1097/00006534-199911000-00011>

28. Dong, C. B., Zheng, S., Shen, C., & Li, H. (2014). Mandible traction with wires for the treatment of upper airway obstruction caused by Pierre Robin sequence in Chinese infants: Preliminary findings. *Journal of Cranio-Maxillofacial Surgery*, 42(7), 1122–1127. <https://doi.org/10.1016/j.jcms.2014.01.042>

29. Hidalgo D. A. (1989). Fibula free flap: a new method of mandible reconstruction. *Plastic and reconstructive surgery*, 84(1), 71–79.

30. Foster, R. D., Anthony, J. P., Sharma, A., & Pogrel, M. A. (1999). Vascularized bone flaps vs nonvascularized bone grafts in mandibular reconstruction. *Plastic and Reconstructive Surgery*, 104(2), 371–379. <https://doi.org/10.1097/00006534-199908000-00001>

31. Suyama, Y., Yagi, S., Fukuoka, K., Morita, M., Kinjo, A., Fukuhara, T., Fujiwara, K., Kodani, I., & Osaki, Y. (2022). Risk Factors of Free Flap Complications in Reconstruction for Head and Neck Cancer. *Yonago acta medica*, 65(3), 215–225. <https://doi.org/10.33160/yam.2022.08.007>

32. Thomaz, F. B., Marchiori, E., Guimarães, A. N., de Magalhães, I. F., Magalhães, F. V., Gonçalves, L. P., & Domingues, R. C. (2009). Primary mediastinal liposarcoma - computed tomography and pathological findings: a case report. *Cases journal*, 2, 8703. <https://doi.org/10.4076/1757-1626-2-8703>

33. Guo, B., Zhang, W., Tume, R. K., Hudson, N. J., Huang, F., Yin, Y., & Zhou, G. (2016). Disorder of endoplasmic reticulum calcium channel components is associated with the increased apoptotic potential in pale, soft, exudative pork. *Meat science*, 115, 34–40. <https://doi.org/10.1016/j.meatsci.2016.01.003>

34. Coyle, M. J., Main, B., Hughes, C., Craven, R., Alexander, R., Porter, G., & Thomas, S. (2016). Enhanced recovery after surgery (ERAS) for head and neck oncology patients. *Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery*, 41(2), 118–126. <https://doi.org/10.1111/coa.12482>

35. Hartmann, S., Döring, C., Agostinelli, C., Portscher-Kim, S. J., Lonardi, S., Lorenzi, L., Fuligni, F., Martinez, D., Mehta, J., Borges, A., Hackstein, H., Kippenberger, S., Piccaluga, P. P., Simonitsch-Klupp, I., Cabeçadas, J., Campo, E., Facchetti, F., Pileri, S. A., & Hansmann, M. L. (2016). miRNA expression profiling divides follicular dendritic cell sarcomas into two groups, related to fibroblasts and myopericytomas or Castleman's disease. *European journal of cancer (Oxford, England:1990)*, 64, 159–166. <https://doi.org/10.1016/j.ejca.2016.06.004>

36. Sun, G. H., Harmych, B. M., Dickson, J. M., Gonzalez del Rey, J. A., Myer, C. M., 3rd, & Greinwald, J. H., Jr (2011). Characteristics of children diagnosed as having coagulopathies following posttonsillectomy bleeding. *Archives of otolaryngology--head & neck surgery*, 137(1), 65–68. <https://doi.org/10.1001/archoto.2010.227>

37. Graboyes, E. M., Garrett-Mayer, E., Ellis, M. A., Sharma, A. K., Wahlquist, A. E., Lentsch, E. J., Nussenbaum, B., & Day, T. A. (2017). Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. *Cancer*, 123(24), 4841–4850. <https://doi.org/10.1002/cncr.30939>

38. Kiyota, N., Tahara, M., Mizusawa, J., Kodaira, T., Fujii, H., Yamazaki, T., Mitani, H., Iwae, S., Fujimoto, Y., Onozawa, Y., Hanai, N., Ogawa, T., Hara, H., Monden, N., Shimura, E., Minami, S., Fujii, T., Tanaka, K., Homma, A.,

Yoshimoto, S., ... Head and Neck Cancer Study Group of the Japan Clinical Oncology Group (JCOG-HNCSG) (2022). Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 40(18), 1980–1990. <https://doi.org/10.1200/JCO.21.01293>

39. Deasy, J. O., Moiseenko, V., Marks, L., Chao, K. S., Nam, J., & Eisbruch, A. (2010). Radiotherapy dose-volume effects on salivary gland function. *International journal of radiation oncology, biology, physics*, 76(3 Suppl), S58–S63. <https://doi.org/10.1016/j.ijrobp.2009.06.090>

40. Biau, J., Lapeyre, M., Troussier, I., Budach, W., Giralt, J., Grau, C., Kazmierska, J., Langendijk, J. A., Ozsahin, M., O'Sullivan, B., Bourhis, J., & Grégoire, V. (2019). Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*, 134, 1–9. <https://doi.org/10.1016/j.radonc.2019.01.018>

41. Patil, V. M., Noronha, V., Joshi, A., Muddu, V. K., Gulia, S., Bhosale, B., Arya, S., Juvekar, S., Chaturvedi, P., Chaukar, D. A., Pai, P., D'Cruz, A., & Prabhash, K. (2013). Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: does it make a difference?. *Indian journal of cancer*, 50(1), 1–8. <https://doi.org/10.4103/0019-509X.112263>

42. Noronha, V., Dhanawat, A., Patil, V. M., Menon, N., Singh, A. K., Chaturvedi, P., Pai, P., Chaukar, D., Laskar, S. G., & Prabhash, K. (2024). Long-term outcomes of neo-adjuvant chemotherapy on borderline resectable oral cavity cancers: Real-world data of 3266 patients and implications for clinical practice. *Oral oncology*, 148, 106633. <https://doi.org/10.1016/j.oraloncology.2023.106633>

43. Uppaluri, R., Campbell, K. M., Egloff, A. M., Zolkind, P., Skidmore, Z. L., Nussenbaum, B., Paniello, R. C., Rich, J. T., Jackson, R., Pipkorn, P., Michel, L. S., Ley, J., Oppelt, P., Dunn, G. P., Barnell, E. K., Spies, N. C., Lin, T., Li, T., Mulder, D. T., Hanna, Y., ... Adkins, D. R. (2020). Neoadjuvant and Adjuvant Pembrolizumab in Resectable Locally Advanced, Human Papillomavirus-Unrelated Head and Neck Cancer: A Multicenter, Phase II Trial. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 26(19), 5140–5152. <https://doi.org/10.1158/1078-0432.CCR-20-1695>

44. Haddad, R., Fayette, J., Teixeira, M., Prabhash, K., Mesia, R., Kawecki, A., Dechaphunkul, A., Dinis, J., Guo, Y., Masuda, M., Hsieh, C. Y., Ghi, M. G., Vaz de Melo Sette, C., Harrington, K., Tahara, M., Saba, N. F., Lau, A., Jiang, T., Yan, Y., Ballinger, M., ... Wong, D. J. (2025). Atezolizumab in High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A Randomized Clinical Trial. *JAMA*, 333(18), 1599–1607. <https://doi.org/10.1001/jama.2025.1483>

45. Burtneess, B., Harrington, K. J., Greil, R., Soulières, D., Tahara, M., de Castro, G., Jr, Psyrri, A., Basté, N., Neupane, P., Bratland, Å., Fuereder, T., Hughes, B. G. M., Mesía, R., Ngamphaiboon, N., Rordorf, T., Wan Ishak, W. Z., Hong, R. L., González Mendoza, R., Roy, A., Zhang, Y., ... KEYNOTE-048 Investigators (2019). Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet (London, England)*, 394(10212), 1915–1928. [https://doi.org/10.1016/S0140-6736\(19\)32591-7](https://doi.org/10.1016/S0140-6736(19)32591-7)

46. Tahara, M., Greil, R., Rischin, D., Harrington, K. J., Burtneess, B., de Castro, G., Psyrri, A., Braña, I., Neupane, P., Bratland, Å., Fuereder, T., Hughes, B. G. M., Mesía, R., Ngamphaiboon, N., Rordorf, T., Ishak, W. Z. W., Lin, J., Gumuscu, B., Lerman, N., & Soulières, D. (2025). Pembrolizumab with or without chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma: 5-year follow-up from the randomized phase III KEYNOTE-048 study. *European journal of cancer (Oxford, England : 1990)*, 221, 115395. <https://doi.org/10.1016/j.ejca.2025.115395>

47. Ferris, R. L., Blumenschein, G., Jr, Fayette, J., Guigay, J., Colevas, A. D., Licitra, L., Harrington, K., Kasper, S., Vokes, E. E., Even, C., Worden, F., Saba, N. F., Iglesias Docampo, L. C., Haddad, R., Rordorf, T., Kiyota, N., Tahara, M., Monga, M., Lynch, M., Geese, W. J., ... Gillison, M. L. (2016). Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *The New England journal of medicine*, 375(19), 1856–1867. <https://doi.org/10.1056/NEJMoa1602252>

48. Mortensen, H. R., et al. (2015). Prophylactic swallowing exercises during CRT: randomized trial. *Head & Neck*, 37(9), 1400–1408. <https://doi.org/10.1002/hed.23759>

49. Nutting, C., McDowell, L., Harrington, K. J., et al. (2023). DARS: dysphagia-optimized IMRT vs standard RT. *Lancet Oncology*, 24(10), —. [https://doi.org/10.1016/S1470-2045\(23\)00265-6](https://doi.org/10.1016/S1470-2045(23)00265-6)
50. Bhandare, N., Kennedy, L., Malyapa, R. S., et al. (2007). Hypothyroidism after neck RT: dose-response analysis. *International Journal of Radiation Oncology, Biology, Physics*, 68(4), 1131-1139. <https://doi.org/10.1016/j.ijrobp.2007.01.029>
51. Rooney, M. K., et al. (2023). Review of hypothyroidism post-RT in HNC. *Cancers (Basel)*, 15, —. <https://doi.org/10.3390/cancers15133433>
52. Chattaraj, A., Paken, J., et al. (2023). Review of cisplatin ototoxicity monitoring. *Cancers (Basel)*, 15(15), —. <https://doi.org/10.3390/cancers15153818>
53. Chen, A. Y., Frankowski, R., Bishop-Lee, B., et al. (2001). MD Anderson Dysphagia Inventory development. *Archives of Otolaryngology – Head & Neck Surgery*, 127(7), 870-876. <https://doi.org/10.1001/archotol.127.7.870>
54. Lajolo, C., Gioco, G., et al. (2021). Oral surgery & ORN: systematic review. *Healthcare (Basel)*, 9(11), 1519. <https://doi.org/10.3390/healthcare9111519>
55. Corrao, G., et al. (2023). Oral surgery in irradiated patients: update. *Cancers (Basel)*, 15(9), —. <https://doi.org/10.3390/cancers15092523>
56. Santucci, N. M., et al. (2021). Adherence to ototoxicity monitoring guidelines with cisplatin. *Journal of Oncology Pharmacy Practice*, 27(8), 1930-1939. <https://doi.org/10.1177/10781552211001626>
57. Lee, D. S., et al. (2023). Audiologic follow-up during cisplatin-RT for HNC. *Supportive Care in Cancer*, 31, —. <https://doi.org/10.1007/s00520-023-07923-7>
58. Gambacorta, V., et al. (2023). Monitoring cisplatin ototoxicity: survey. *European Archives of Oto-Rhino-Laryngology*, 280(12), 5341-5350. <https://doi.org/10.1007/s00405-023-07924-2>
59. Rogers, S. N., Lowe, D., Brown, J. S., & Vaughan, E. D. (1999). The University of Washington head and neck cancer measure as a predictor of outcome following primary surgery for oral cancer. *Head & neck*, 21(5), 394-401. [https://doi.org/10.1002/\(sici\)1097-0347\(199908\)21:5<394::aid-hed3>3.0.co;2-q](https://doi.org/10.1002/(sici)1097-0347(199908)21:5<394::aid-hed3>3.0.co;2-q)
60. Hanna, G. J., et al. (2024). Tumor-informed ctDNA MRD in nonviral HNSCC. *Clinical Cancer Research*, 30. <https://doi.org/10.1158/1078-0432.CCR-23-2684>
61. Chera, B. S., Kumar, S., et al. (2020). Plasma ctHPV DNA for surveillance in HPV-positive OPSCC. *Journal of Clinical Oncology*, 38(10), 1050-1058. <https://doi.org/10.1200/JCO.19.02444>
62. Brandt, A., Thiele, B., Schultheiß, C., Daetwyler, E., & Binder, M. (2023). Circulating Tumor DNA in Head and Neck Squamous Cell Carcinoma. *Cancers*, 15(7), 2051. <https://doi.org/10.3390/cancers15072051>
63. Lele, S. J., Adilbay, D., Lewis, E., Pang, J., Asarkar, A. A., & Nathan, C. O. (2024). ctDNA as an Adjunct to Posttreatment PET for Head and Neck Cancer Recurrence Risk Assessment. *Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery*, 171(2), 439-444. <https://doi.org/10.1002/ohn.760>
64. Franzese, C., Botta, F., et al. (2023). Role of AI in RT workflow (contouring/planning). *Cancers (Basel)*, 15. <https://doi.org/10.3390/cancers15102615>
65. Liu, P., et al. (2023). DL auto-contouring of H&N OARs: systematic review. *Cancers (Basel)*, 15. <https://doi.org/10.3390/cancers15215118>
66. Erdur, A. C., Rusche, D., Scholz, D., Kiechle, J., Fischer, S., Llorián-Salvador, Ó., Buchner, J. A., Nguyen, M. Q., Etzel, L., Weidner, J., Metz, M. C., Wiestler, B., Schnabel, J., Rueckert, D., Combs, S. E., & Peeken, J. C. (2025). Deep learning for autosegmentation for radiotherapy treatment planning: State-of-the-art and novel perspectives. *Strahlentherapie und Onkologie: Organ der Deutschen Röntgengesellschaft ... [et al]*, 201(3), 236-254. <https://doi.org/10.1007/s00066-024-02262-2>

Ауыз қуысының жергілікті дамыған жалпақ жасушалы карциномасында хирургиялық араласумен байланысты периоперативтік мультимодальды секвенирлеу: Қазіргі жағдайы және болашағы

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Түйіндеме

Хирургиялық емдеу ауыз қуысының резекцияланатын жергілікті дамыған жалпақ жасушалы карциномасының негізі болып қала береді. Оңтайлы нәтижелер науқасты дұрыс таңдауға, патологиялық қауіпті болжаумен жүретін онкологиялық экстирпацияға, сондай-ақ, дер кезінде жасалған, реконструктивті стратегияға сүйенген, жүйелік терапиямен қатар жүретін (немесе бұл терапиясыз) адьювантты сәулелік терапияға және соңғы жылдары жақсы даму үстіндегі неоадьювантты/адьювантты иммунотерапияға байланысты. Біз келесі тақырыптар бойынша беделді журналдар мен нұсқаулықтардан I-III деңгейдегі дәлелдер мен ағымдағы консенсусты синтездедік: кезеңді нақтылау, инвазия шегінің/тереңдігінің стандарттары, науқастарды жоспарлы басқару, отадан кейінгі сәулелік терапияның/қатар жүретін химиотерапияның уақыты/техникасы және отадан кейінгі қалпына келуді жақсарту, сондай-ақ периоперативтік жүйелік терапия.

Маңызды рандомизацияланған сынақтар жоғары қауіпті отадан кейінгі когорталарда (оң шегі және/немесе экстранодальды таралу) сәулелік терапияға жоғары дозалы цисплатинді қосу жергілікті аймақтық бақылауды және аурусыз өмір сүруді жақсартатынын көрсетті. Цисплатинді (40 мг/м²) апта сайын енгізудің оны 100 мг/м² дозасында 3 апта бойына енгізуден әсері кем емес әрі уыттылығы аз. Мойынның cN0 кезіндегі жоспарлы емі лимфа түйіндердегі рецидивтен кейін терапиялық мойын диссекциясымен салыстырғанда өмір сүруді жақсартады, ал шолғыншы лимфа түйінінің биопсиясы онкологиялық тұрғыдан cT1-2N0 ауруында мойынның селективті диссекциясына баламалы екені анықталды әрі ерте аурушаңдық деңгейі төмен екені белгілі болды. Отадан кейінгі қарқындылығы модуляцияланған сәулелік терапия 3D-CRT-мен салыстырғанда ксеростомияны азайтады. Отадан кейін ~6 аптадан астам кідірістер және емдеудің аяқталу уақытының ұзаруы науқастардың өмір сүру сапасының нашарлауына әкеледі. Ерте дәлелдер бас пен мойынның резекцияланатын жалпақ жасушалы карциномасында периоперативтік PD-1 анти-терапиясының тиімділігін растайды. Ал стандартты емнен кейінгі адьювантты PD-L1 анти-монотерапиясы теріс нәтиже берді. Ақаудың сыныбына бейімделген, мүше қызметін сақтау мен мен адьювантты терапияға дайындықты басым мақсатқа алған реконструкция тері қиындысының тұрақтылығын сақтап, отадан кейінгі қалпына келуді жеделдетуді және қауіпсіздікке нұқсан келтірмей ауруханада болу ұзақтығын қысқартуды қамтамасыз етеді. Хирургиялық жолмен бекітілген, уақытқа сезімтал және тәуекелге бейімделген емдеу тізбегі, соның ішінде мойынның кеңейтілген хирургиялық емдеу әдістері, отадан кейінгі қарқындылыққа модуляцияланған сәулелік терапия, химиотерапиямен отадан кейінгі қалпына келтіру және селективті иммунотерапия ауыз қуысының кеңейтілген жалпақ жасушалы карциномасын емдеудің ең жақсы қазіргі нәтижелерін береді. Жүргізіліп жатқан зерттеулер периоперативтік иммунотерапияны біріктірудің тиімділігін, орташа қауіп жағдайындағы деэскалацияны және биомаркерді қолдану көрсеткіштерін нақтылайды.

Түйін сөздер: ауыз қуысының жалпақ жасушалы карциномасы, хирургия, мойын диссекциясы, инвазия тереңдігі, отадан кейінгі сәулелік терапия.

Периоперационное мультимодальное секвенирование с привязкой к хирургическому вмешательству при местно-распространенном плоскоклеточном раке полости рта: Современное состояние и перспективы

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Резюме

Хирургическое лечение остается краеугольным камнем при резектабельном местно-распространенном плоскоклеточном раке полости рта. Оптимальные результаты зависят от точного отбора пациентов, онкологической экстирпации со стратификацией патологического риска, своевременной адъювантной лучевой терапии с сопутствующей системной терапией или без нее, основанных на фактических данных реконструктивных стратегий и, в последнее время, хорошо разработанной неоадъювантной/адъювантной иммунотерапии. Мы синтезировали доказательства I–III уровня и современный консенсус из авторитетных журналов и руководств по следующим вопросам: уточнение стадирования, стандарты края/глубины инвазии, плановое ведение пациентов с заболеваниями шеи, сроки/техника послеоперационной лучевой терапии/послеоперационной сопутствующей химиолучевой терапии и ускоренное восстановление после операции, а также периоперационная системная терапия.

Важные рандомизированные исследования показали, что в послеоперационных когортах высокого риска (положительный край и/или экстранодальное распространение) добавление высокой дозы цисплатина к послеоперационной лучевой терапии улучшает локорегиональный контроль и безрецидивную выживаемость; Еженедельное введение цисплатина (40 мг/м²) не уступает 3 недельному введению 100 мг/м² и менее токсично. Плановое лечение шейного отдела cN0 улучшает выживаемость по сравнению с терапевтической шейной диссекцией после рецидива лимфоузлов, а биопсия сторожевого лимфоузла онкологически эквивалентна селективной шейной диссекции при заболевании cT1–2N0 с меньшей ранней заболеваемостью. Послеоперационная лучевая терапия с модулированной интенсивностью снижает ксеростомию по сравнению с 3D-CRT; задержки более ~6 недель после операции и увеличение времени прохождения курса лечения связаны с худшей выживаемостью. Ранние признаки подтверждают эффективность периоперационной анти-PD-1 терапии при резектабельном плоскоклеточном раке головы и шеи, в то время как адъювантная анти-PD-L1 монотерапия после стандартного лечения оказалась отрицательной. Реконструкция, адаптированная к классу дефекта с приоритетом функции и готовности к адъювантной терапии, обеспечивает высокую выживаемость лоскута, ускоренное восстановление после операции и сокращает продолжительность госпитализации без ущерба для безопасности. Хирургически фиксированная, чувствительная ко времени и адаптируемая к риску последовательность лечения, включающая современные методы лечения заболеваний шеи, послеоперационную лучевую терапию с модулированной интенсивностью, послеоперационную реконструкцию с помощью химиолучевой терапии и селективную иммунотерапию, обеспечивает наилучшие текущие результаты лечения распространенного плоскоклеточного рака полости рта. Продолжающиеся исследования позволяют определить эффективность интеграции периоперационной иммунотерапии, деэскалацию при промежуточном риске и уточнение показаний к применению биомаркеров.

Ключевые слова: плоскоклеточный рак полости рта, хирургическое вмешательство, диссекция шеи, глубина инвазии, послеоперационная лучевая терапия.