12th Annual Otolaryngology Literature Update
Head & Neck Oncology II

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Dr. Kejner is an otorhinolaryngologist/head and neck surgeon dedicated to the treatment of head and neck patients, including those with malignant and benign tumors of the head and neck, including skin, sinus, oral cavity, oropharynx, voice box, neck, and salivary glands as well as the reconstruction of those areas after surgery using local tissue, skin grafts, and free tissue transfer. She also is specialty trained in advanced transoral robotic surgery of the upper aerodigestive tract.

Dr. Kejner completed her undergraduate degree in Biology and Spanish at Wake Forest University, graduating with honors. She enrolled at the University of Michigan Medical School, graduating with honors in service and then went on to an otorhinolaryngology residency at the University of Alabama – Birmingham before pursuing advanced training in fellowship at the University of Pennsylvania. While there, she received further training in head and neck oncology, skull base surgery, transoral robotic surgery, and microvascular free tissue transfer. She is certified by the American Board of Otolaryngology.

Dr. Kejner has published several articles in peer-reviewed journals and several book chapters. She is active in the American Head and Neck Society and is on the board of the American Head and Neck Microvascular Section. She has been an invited panelist and organizer for multiple national and international meetings and has acted as a preceptor at the annual Microvascular Bootcamp. She is a member of the Society of Integrative Oncology. She also speaks fluent Spanish.

Dr. Kejner is interested in medical technology, outcomes research, surgical margins, microvascular reconstruction techniques, head and neck cancer, and improving the quality of life of head and neck cancer survivors

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Arianpour K, Meleca JB, Liu SW, Prendes BL, Ciolek PJ, Genther DJ, Mangie C, Khanna S, Fritz MA. Evaluation of Anterolateral Thigh Fascia Lata Rescue Flap for Mandibular Osteoradionecrosis. JAMA Otolaryngol Head Neck Surg. 2023 Jul 1;149(7):621-627. doi: 10.1001/jamaoto.2023.1089. PMID: 37261824; PMCID: PMC10236321.

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Literature Review

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No disclosures

Delayed in diagnosis of upper aerodigestive tract cancers: A comprehensive review of medical malpractice cases

Christian Fritz [1], Karthik Rajasekaran [1 2]

Affiliations + expand

PMID: 37144329 DOI: 10.1002/hed.27390

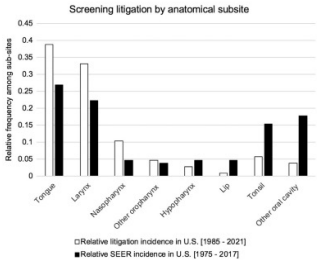
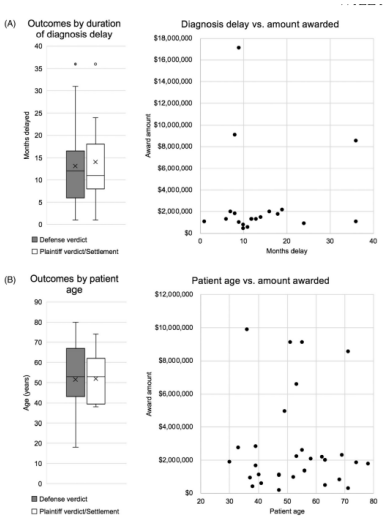


FIGURE 3 Cases by anatomical subsite. Consistent with constraints imposed by SEER reporting, the "other oropharynx" category excludes base of tongue and tonsil cancers. "Other oral cavity" represents the combined SEER incidence of cancer involving the floor of mouth, gum and other oral cavity, and other oral cavity but excludes cancers of the tongue and lips



JAMA Network
JAMA Otolaryngology–Head & Neck Surgery

Original Investigation
June 1, 2023

Evaluation of Anterolateral Thigh Fascia Lata Rescue Flap for Mandibular Osteoradionecrosis

Khashayar Arianpour, MD[1]; Joseph B. Meleca, MD[2]; Sara W. Liu, MD[1]; et al

Author Affiliations | Article Information

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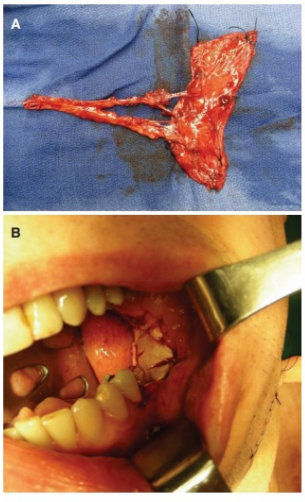


Fig. 2. A and B: An example of (A) a harvested anterolateral thigh fascia lata free flap and (B) an intraoral intraoperative inset using this rescue technique. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

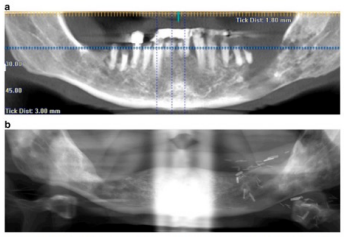
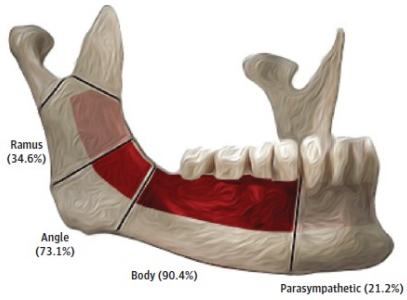


Fig. 4. a) Preoperative panorex imaging showing moderate mandibular osteoradionecrosis with scattered lucencies. b) Postoperative imaging obtained at the 6 month visit shows no evidence of progression of disease. Note the surgical absence of the dentition and the radiopaque surgical clips.

Figure 1. Mandibular Subsite Distribution of ORN Treated With the ALTFL Rescue Flap Procedure



Darker red signifies a higher prevalence of subsite involvement. ALTFL refers to the anterolateral thigh fascia lata and ORN to osteoradionecrosis. This illustration was created by Dr Khashayar Arianpour.

Surgical clinical trials for HPV-positive oropharyngeal carcinoma

Chen Lin[1,2], Daniel D. Sharbel[1] and Michael C. Topf[1]*

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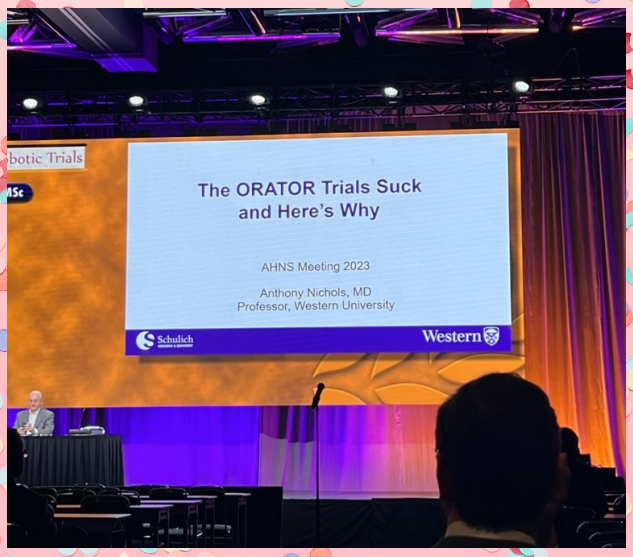
TABLE 1 Surgical clinical trials for HPV-mediated oropharyngeal carcinoma.

	Trial	Phase	Primary location	Status	Eligible patients (AJCC 7th)	Intervention	Primary end point	Results	Other notable findings
Surgical vs nonsurgical trials	ORATOR	II	Canada	Completed	T1-2, N0-2	TORS vs primary RT (70 Gy)	MDADI	80.1 (TORS) vs 86.9 (RT) (p = 0.04)	–
	EORTC 1420	III	Europe	Active	T1-2, N0-1**	TORS/TLM vs primary RT (66-70 Gy)	MDADI	Not available	–
De-escalation trials	E3311	II	United States	Completed	T1-2, N0-2b	TORS/TLM + adjuvant RT (50 Gy vs 60 Gy) for intermediate-risk	2-year PFS	94.9% (50 Gy) vs 96.0% (60 Gy) (p = 0.90)	14% (50 Gy) vs 24% (60 Gy) (p < 0.0001) for >= Grade 3 events
	SIRS	II	Mount Sinai	Completed	T1-2, N0-2b	TORS + adjuvant RT (50 Gy) for intermediate-risk group and TORS + adjuvant RT (56 Gy) + cisplatin for high-risk	PFS, LRF	PFS: 91.3% (low-risk), 86.7% (intermediate-risk), 93.3% (high-risk) LRF: 5 failures	7.4% occult nodal disease in contralateral N0 neck
	ADEPT	III	Washington Univ.	Terminated	ENE with negative margins	Omission of cisplatin for ENE	DFS and LRC	Not available	–
	PATHOS	II/III	United Kingdom	Active	T1-3, N0-2b	TORS/TLM + adjuvant RT (50 Gy vs 60 Gy) for intermediate-risk group and omission of cisplatin for ENE in high-risk group	OS and MDADI	Not available	–
	MC1273	II, single arm	Mayo Clinic	Completed	T1-4a, N0-3	TORS + adjuvant RT (30-36 Gy) + docetaxel	2-year LRC	96.2%	–
	MC1675	III	Mayo Clinic	Completed (not yet published)	T1-3, N0-3	TORS + adjuvant RT (30-36 Gy) + docetaxel vs TORS + adjuvant RT (60 Gy) +/- cisplatin	Adverse events	1.6% (DART) vs 7.1% (SOC) for >= Grade 3 events	2-year PFS in +ENE groups was 78.9% (DART) vs 96.2% (SOC)
	AVOID	II, single arm	Univ. of Penn.	Completed	pT1-2, N1-3	TORS + adjuvant neck RT (60-66 Gy) (primary site spared)	2-year LC	98.30%	Primary site still received mean dose of 37 Gy RT (part of neck treatment field)
	ORATOR2*	III	Canada	Terminated	T1-2, N0-2 (8th edition)	TORS/TLM + adjuvant RT (50 Gy) vs primary RT (60 Gy)	OS	Not available	2 treatment deaths out of 27 surgical patients (hemorrhage and cervical spine osteomyelitis)

*Combination of surgical vs nonsurgical trial with de-escalation protocols.
**T1-2, N0-1 supraglottis and T1-2, N0 hypopharynx also included in trial.



ORATOR trial:

Group1 = TORS + ND, + adjuvant therapy based on pathology,

Group 2=Primary RT with or without chemotherapy

Innovation

- 1st RCT to compare surgical versus nonsurgical standard-of-care treatment for HPV+ OPSCC
- QOL at 1 year, 2 years, and 3 years

Where they missed the mark:

- TLM and TORS included, all patients trached (ie not standardized approach as was in ECOG3311)
- Too short of an interval to assess long term RT toxicity
- Surgical group got XRT for ANY positive nodes (current recommendation 2 or fewer with no adverse can observe)
- Surgical group got chemo for + margins, current recommendation is for re-resection with RT
- No discussion re ENE-micro vs. ENE-macro
- Among 34 surgical patients, only 10 were treated with surgery alone, while 16 received dual modality therapy and 8 received triple modality therapy.
- Comparing the 1-year MDADI scores of ORATOR and ECOG 3311 (E3311), the surgery + RT scores were very similar between both studies (79.1 at 50 Gy and 78.8 at 60 Gy for E3311 vs 78.5 for ORATOR), but the surgery alone score was over 10 points higher in E3311 (94.7 vs 82.8 for ORATOR) (26, 27).

EORTC 1420 Trial: "Best of" study, is a RCT comparing the "Best of" RT and "Best of" surgery in patients with early-stage oropharyngeal, supraglottic, and hypopharyngeal squamous cell carcinoma

Innovation

- Similar to ORATOR trial comparing RT and surgery BUT …
- One issue: no specification on dose for adjuvant nor on criteria for adjuvant therapy

Why this is better than ORATOR

- Includes anatomic subsites outside of the OP,
- Includes TORS, TLM, and traditional
- Rigorous quality assurance program
- Excludes N2 disease & recommendation for trach
- Return to OR for re-resection of margins when feasible

ECOG 3311

Dr. Newman will talk about this one! *Exciting!*

SIRS: Sinai Robotic Trial
non-randomized study that evaluated the role of de-escalated adjuvant chemoradiotherapy following TORS and neck dissection for treatment of HPV+ OPSCC

Innovations

- Low-risk patients (T1-2 with negative margins, no LVI/PNI/ ENE) were stratified to surveillance (group 1, n = 24).
- Intermediate risk patients (+LVI/PNI, ≤ 1 mm ENE) underwent adjuvant RT at 50 Gy (group 2, n = 14).
- High-risk patients (positive margins, ≥1 mm ENE, >3 positive nodes, contralateral/supraclavicular nodes were treated with 56 Gy + cisplatin (group 3, n = 15).
- Since all patients underwent bilateral neck dissection regardless of primary site, the authors were able to report on the rate of occult nodal disease in the contralateral cN0 neck - 4 of 54 patients (7.4%). Of these 4 patients, 2 were tonsil and 2 were base of tongue

Things to consider

- All patients underwent bilateral selective neck dissections and ipsilateral lingual artery ligation if tongue was resected.
- Patients with >20 pack year smoking histories were excluded.
- Negative margins were defined as >1mm for tonsil and >3 mm for base of tongue

The Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT)

Innovation

- All patients were treated with transoral surgery (TORS or TLM) and neck dissection.
- Negative margins at the primary site, but with ENE were included in the study
- Treated with adjuvant radiation at 60 Gy with or without cisplatin.
- Patients were given the option to be either randomized (physician chose the study arm) or nonrandomized (patient chose the study arm)

No results yet!

PATHOS: The Post-operative Adjuvant Treatment for HPV-positive Tumors: treatment de-intensification for both radiation and chemotherapy in patients treated surgically for HPV+ OPSCC

Innovations

- Combo of ADEPT and ECOG3311
- The primary end point of the phase II study is MDADI at 1-year, while the primary end points of the phase III study are overall survival and MDADI
- T1-3, N0-2b (AJCC 7th edition) or T1-3, N0-1 (AJCC 8th edition) HPV+ OPSCC who undergo transoral surgery (TORS or TLM) and neck dissection are risk stratified based on pathologic findings
- Low-risk patients: observation
- Intermediate-risk patients (T1-2 with positive PNI/positive LVI/close margins (1-5 mm) or N2a-b) are randomized to 50 Gy or 60 Gy, similar to E3311.
- High-risk patients (positive margins (<1 mm) or ENE) are randomized to 60 Gy with or without concurrent cisplatin, similar to ADEPT.

Results still pending

The phase II portion of the trial was completed at multiple sites in the United Kingdom from 2015 to 2018 with results yet to be published. The trial transitioned directly to Phase III in 2018 with recruitment of 1,100 patients expected to complete by the end of 2022 followed by a 4-year follow up period until 2026. The phase III trial is still conducted predominantly in the UK with additional centers in Europe, Australia, and the US

MC1273 (NCT01932697) was a phase II single arm, prospective study evaluating a significant dose-reduction in adjuvant radiation (30-36 Gy) after surgical resection

Innovation

- All patients (n = 80) received de-escalated adjuvant radiation and chemotherapy after undergoing TORS with negative margins and neck dissection.
- Low-risk patients and those with >10 pack year smoking history were excluded from the trial.
- Intermediaterisk (n = 37) included ≥T3, PVI/LVI, ≥2 lymph nodes, or any node >3 cm, received 30 Gy adjuvant RT.
- Highrisk (n = 43) was determined by the presence of ENE, and this group received 36 Gy.
- Patients were treated with twice-per-day fractionated radiotherapy for 2 weeks. The 2-year LRC, PFS, and OS were 96.2%, 91.1%, and 98.7%

Interesting outcomes

- The regimen was well tolerated by patients. QOL and swallowing function were mildly improved at post-RT compared to pre-RT, however, swallowing function was not measured prior to surgery.
- With the reduction in radiation and chemotherapy, the average cost of treatment dropped from $57,845 for standard-of-care adjuvant CRT to $45,884. This represented a 33% reduction in cost of RT and 21% reduction in overall cost.
- One concern of the MC1273 study was that intermediate-risk patients who would typically receive dual modality therapy were treated with triple modality therapy. Although all patients received chemotherapy, the investigators chose docetaxel over cisplatin due to favorable results of RTOG 0234 showing improved survival and tolerance of therapy

MC1675 trial, also known as De-escalated Adjuvant Radiation Therapy for HPV associated Oropharynx Cancer (DART-HPV): p, RCT (n = 194) in which a control arm (n = 115) using standard-of-care adjuvant RT (60 Gy) was compared to the de-escalated therapy group

Innovation

- T1-3, N0-3 HPV+ OPSCC underwent TORS and neck dissection.
- Intermediate-risk patients were treated with adjuvant RT to 60 Gy in the control arm
- Study arm received 30 Gy plus docetaxel based on MC1273.
- High-risk ENE control arm received 60 Gy plus cisplatin while the study arm received 36 Gy plus docetaxel.

ENE and N2 disease important in this trial

- The DART group had significantly less toxicity (1.6% vs 7.1% for ≥Grade 3 adverse events) including far less patients who required a feeding tube (1.6% vs 27.4%).
- Swallowing function and QOL were also improved in the DART group. Regarding 2-year OS and LRC, both groups were similar. However, 2-year PFS in the DART group was 86.5% while the standard-of-care group was 95.1%.
- While PFS for both intermediate-risk groups was similar (97.6% for DART and 93.3% for SOC), there were significant differences in PFS within the high-risk ENE groups (78.9% DART vs 96.2% standard-of-care), particularly in patients with pN2 status (AJCC 8th edition).
- The combination of ENE and pN2 showed significant differences between treatment groups for PFS (42.9% DART vs 100% standard of care) and LRC (77% vs 100%). These results showed that de-escalation therapy can be effective in intermediate-risk patients without ENE.

The Alternative Volumes of Oropharyngeal Irradiation for De-intensification (AVOID) trial was a phase II single arm, prospective study investigating the sparing of adjuvant radiation to the primary site after surgical resection

Innovation

- p16+ OPSCC who had undergone TORS plus neck dissection and required adjuvant therapy based on lymph nodes and ENE. Patients had to have negative margins (≥2 mm) without LVI/PNI
- Patients received standard-of-care 60-66 Gy adjuvant RT to the neck ONLY

Interesting findings

- High 2-year local control of 98.3% (1 local recurrence out of 60 patients) and OS of 100%.
- 3.3% (2 patients) required a feeding tube during treatment, but both patients had them removed by study completion
- 3.3% (2 patients) had soft tissue necrosis within the primary resection bed 3 months after radiation.
- Although the primary tumor was spared of direct adjuvant therapy, the wound bed still received a mean dose of radiation received by the primary site was 37 Gy

ORATOR2 (NCT03210103) was the follow up, phase III RCT to investigate treatment de-escalation in surgical and nonsurgical approaches for HPV+ OPSCC

Ended early

Planned accrual was 140 patients, however the trial was terminated in 2020 after 2 treatment-related deaths in the surgical arm.

Only 61 total patients had been enrolled.

Of 27 patients who underwent surgery, there were 3 total deaths.

Of the 2 treatment-related surgical deaths, one death was secondary to oropharyngeal bleeding on postoperative day 4 in a patient with a tracheostomy, and the other death was related to cervical spine osteomyelitis following adjuvant radiotherapy. The third death was due to a myocardial infarction at 8.5 months in a patient who received adjuvant RT and was deemed not to be treatment-related