Surgical margins: A head and neck surgeon's perspective

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Objectives

1. Understand the different methods for margin sampling in the head and neck*
2. Understand the important relationship between the surgeon and pathology team with regards to specimen management
3. Understand the oncologic prognostic implications for margin status in oral cavity cancers including recurrence and survival

   -- Tongue cancer depth of invasion

*mucosal based H&N disease

Importance

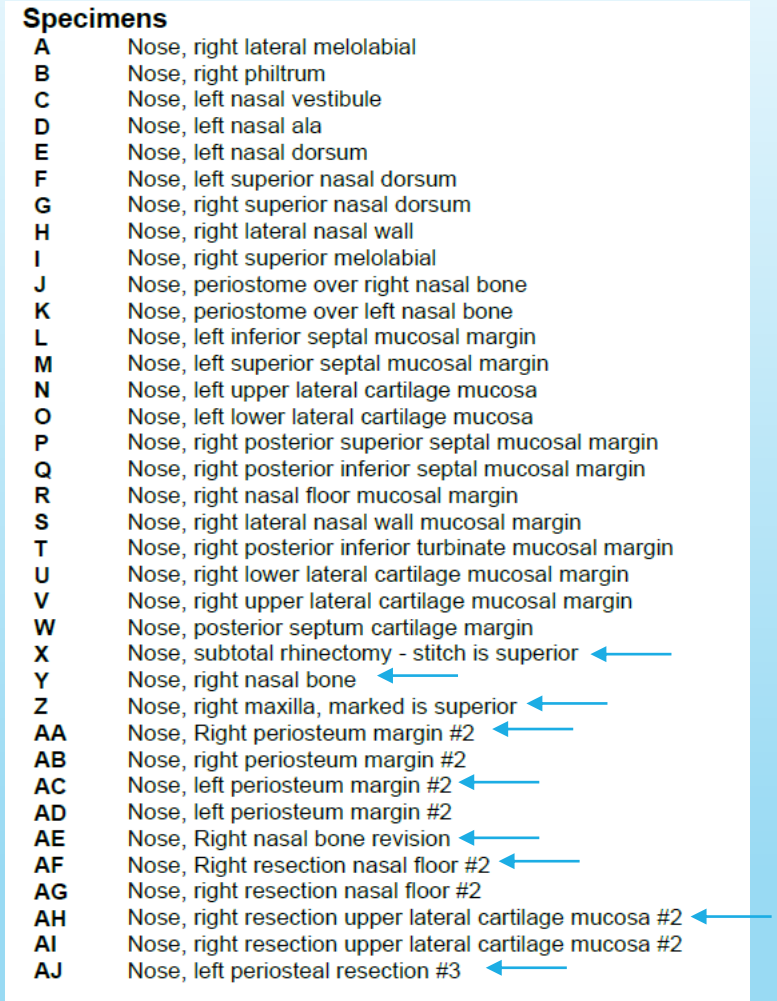
Why does this matter?

Otolaryngology: highest volume of frozen sections

Urken et al 2023:

- 1 academic center record 1517 frozen sections by otolaryngology in 1 year
- 37% of all frozen in 1 yr

Negative margins achieved in 50-80% of patients treated in cancer centers (Amit et al)



Specimens

A	Nose, right lateral melolabial
B	Nose, right philtrum
C	Nose, left nasal vestibule
D	Nose, left nasal ala
E	Nose, left nasal dorsum
F	Nose, left superior nasal dorsum
G	Nose, right superior nasal dorsum
H	Nose, right lateral nasal wall
I	Nose, right superior melolabial
J	Nose, periostome over right nasal bone
K	Nose, periostome over left nasal bone
L	Nose, left inferior septal mucosal margin
M	Nose, left superior septal mucosal margin
N	Nose, left upper lateral cartilage mucosa
O	Nose, left lower lateral cartilage mucosa
P	Nose, right posterior superior septal mucosal margin
Q	Nose, right posterior inferior septal mucosal margin
R	Nose, right nasal floor mucosal margin
S	Nose, right lateral nasal wall mucosal margin
T	Nose, right posterior inferior turbinate mucosal margin
U	Nose, right lower lateral cartilage mucosal margin
V	Nose, right upper lateral cartilage mucosal margin
W	Nose, posterior septum cartilage margin
X	Nose, subtotal rhinectomy - stitch is superior
Y	Nose, right nasal bone
Z	Nose, right maxilla, marked is superior
AA	Nose, Right periosteum margin #2
AB	Nose, right periosteum margin #2
AC	Nose, left periosteum margin #2
AD	Nose, left periosteum margin #2
AE	Nose, Right nasal bone revision
AF	Nose, Right resection nasal floor #2
AG	Nose, right resection nasal floor #2
AH	Nose, right resection upper lateral cartilage mucosa #2
AI	Nose, right resection upper lateral cartilage mucosa #2
AJ	Nose, left periosteal resection #3

9/36 = permanent
27/36 = frozen

Amit et al. *Head & Neck*. 2016;38(S1).
Urken et al. *Oral Oncology*. 2023;143:106445.

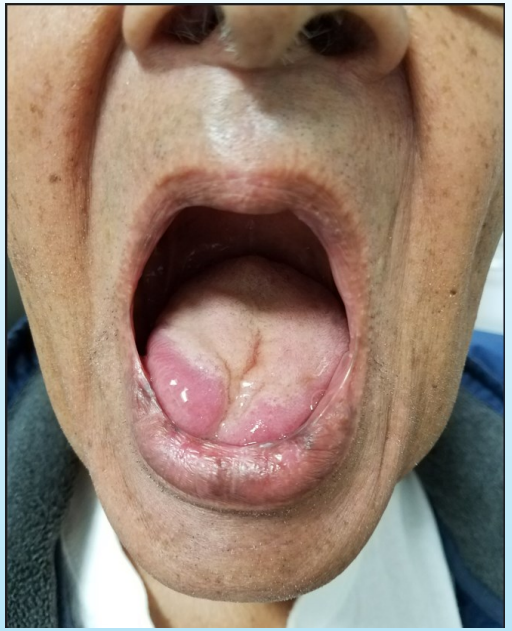
Surgeon margin accuracy

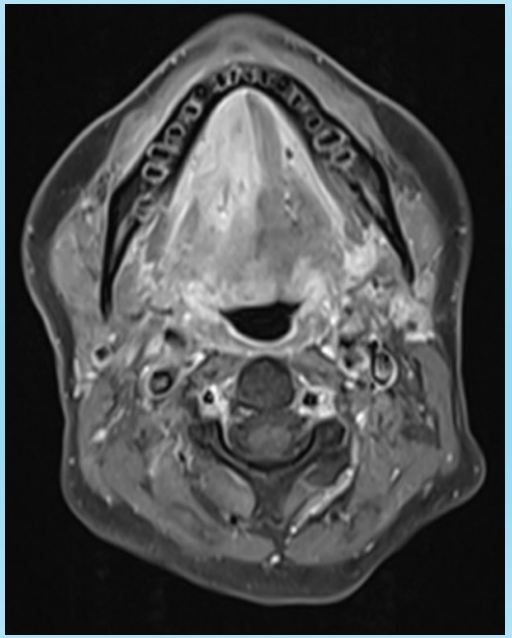
Surgical experience and acumen for mucosal margin:

- *Sensitivity 88.9%*
- *Specificity 81.1%*

Surgical performance deep margin:

- *17% positive of cases in oral cancer*





Higginson et al. *Oral Oncology*. 2023;142:106419.

Clear margins in surgical oncology

Reduce risk of local recurrence

Improve survival

Determine need for adjuvant therapy

Positive margins (and ENE) = high risk features, require adjuvant chemoradiation

Balance preservation of uninvolved tissue for function, QOL, social interactions

Aim for 1 cm surgical margin to get 5 mm margin (25-75% tissue shrinkage) – depend on location

Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.
Sunkara et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(4):317.
Hamman et al. *The Laryngoscope*. 2022;132(2):307-321.
Urken et al. *Oral Oncology*. 2023;143:106445.

Specimen orientation

Pathologist perspective

College of American Pathologists protocol: specify resection margins for H&N cancer be reported as location of positive margin and location and distance of closest uninvolved margins

Goal: pathology report that accurately reflects the margin status

- No standard method of margin analysis

"Only when the pathologist knows specifically where the frozen-section tissue was sampled from before final specimen sectioning can the final pathology report be reliable."

Black et al. *Cancer*. 2006;107(12):2792-2800.

Specimen orientation

Small resections – orient with suture

Large or complicated resections – may require surgeon handoff to pathologist (PA)

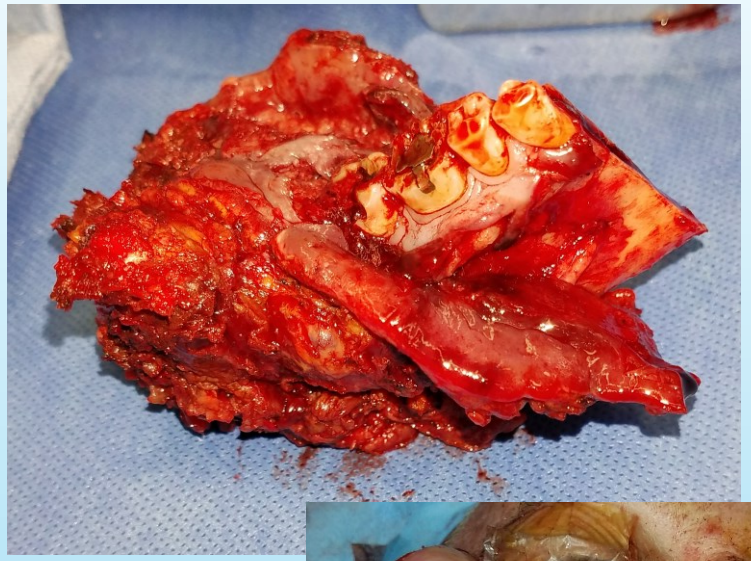
- *Recommend face to face interaction*

Translate complex 3D resection into 2D map

Different inking if section has more than 1 margin

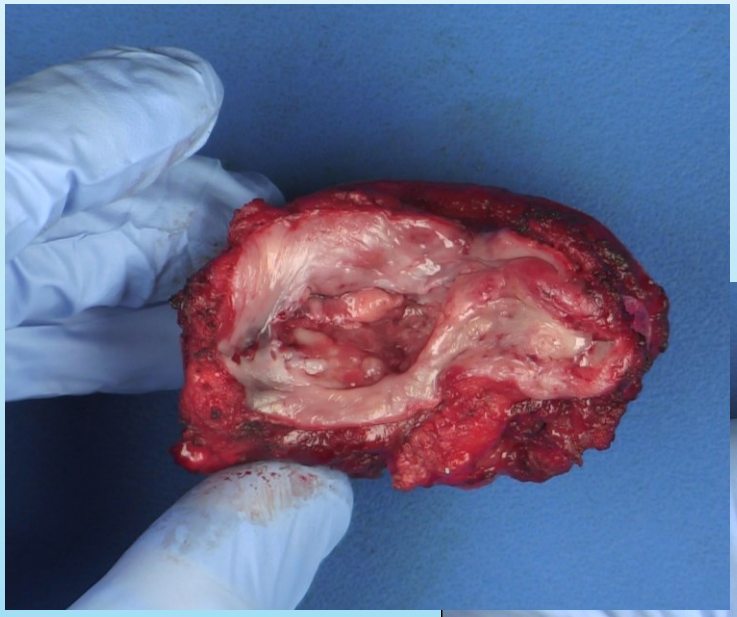
Identify intraoperative non-margin tissue tears or cuts

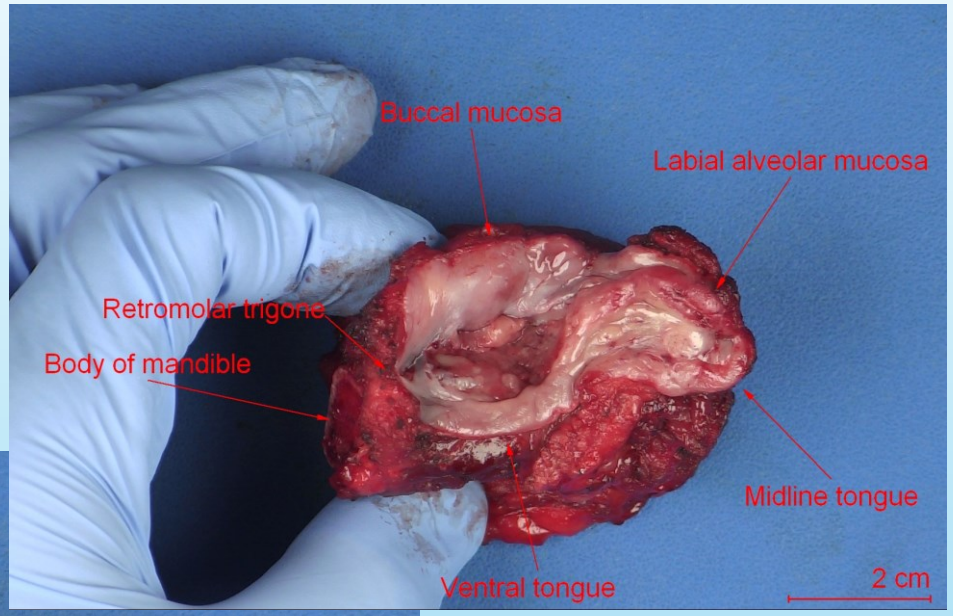
- *Ink in different color*

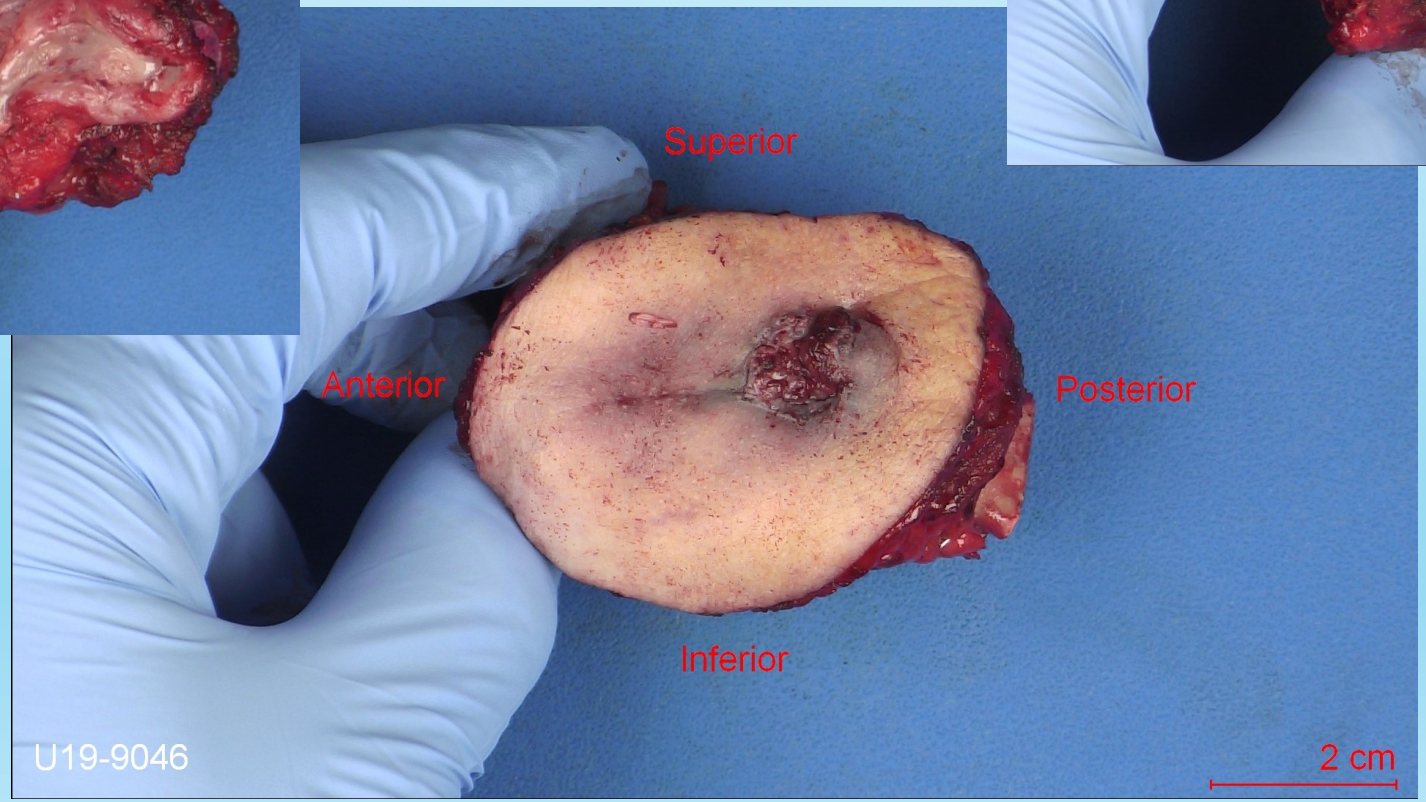


Hinni et al. *Head Neck*. 2013;35(9):1362-1370.

Specimen orientation







Intraoperative margin assessment

Intraoperative margin assessment

Studies related to clinical benefit confounded

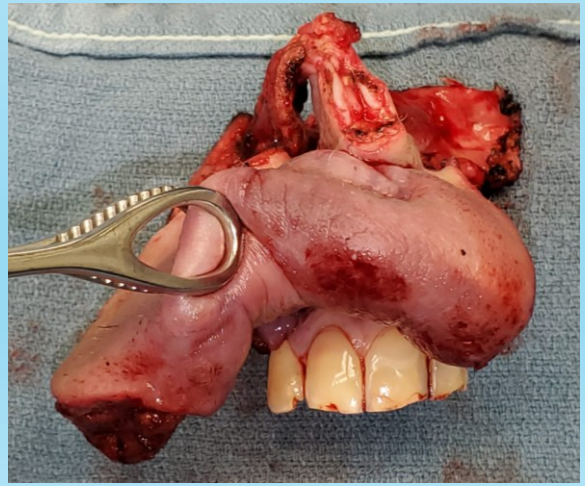
- Tumor size, complexity of resection
- Number and tissue type of margins examined
- Surgeon approach to margin
- Histopathologic technique

Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.

Intraoperative margin assessment

- Specimen-driven
  - Surgeon orients specimen and identifies margin in person for pathology (or PA)
  - Margins removed from main specimen and evaluate microscopically
  - Correlate concerning margins to original location on resection
  - Benefits: better correlation with final margin status, reduced local relapse, improved survival

- Defect (tumor bed)-driven
  - Margin removed from resection cavity by surgeon
  - Benefits: surgeon knows exact site and size



Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.

Tumor margins

Piecemeal resections → fragment specimen

Compare specimen driven approach vs defect driven approach (vs no tumor bed assessment)

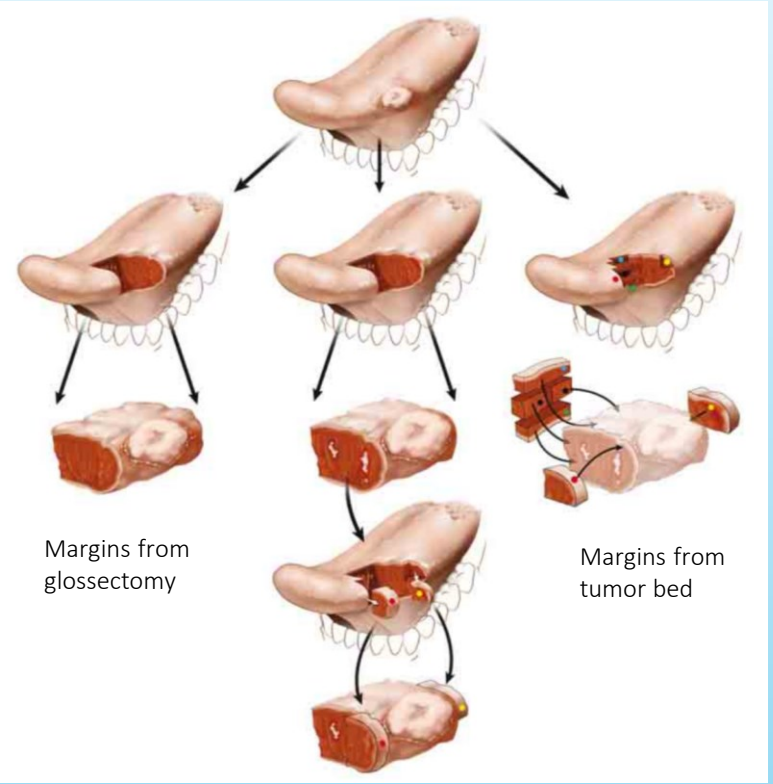
Positive margins lowest in group 1, closest margins in group 2

3 yr LR free survival worse in group 3

3 yrs: positive glossectomy margins worse LR free survival compared to negative glossectomy margins, tumor bed margins no prognostic value

Tumor bed margin: 24% sensitive, 92% specific for detecting positive margin

Difficult to return to tumor bed and resect exact location: surgeons off by ~1 cm in 1/3 of re-resection attempts



Maxwell et al. *JAMA Otolaryngol Head Neck Surg*. 2015. 141(12): 1104-1110.

Tumor margins in oral cavity

- Retrospective review intraoperative margins from oral cavity tumor bed
- Frozen section accuracy 99%, 97% sensitivity, nearly 100% specificity;
  - 14 false-negative diagnoses, 8 false-positive diagnoses
- LR rates negative vs positive margins (specimen margin): 13% vs 45%
- Tumor specimen margins significantly associated with LR, initial intraoperative frozen margins and final operative margins not significantly associated with LR
- Tumor bed frozen margins do not independently predict prognosis
- Achieving negative margin from additional tissue resection not associated with improved LR rate or overall prognosis
- Main specimen margin most strongly predictive regardless of whether margin ultimately cleared with additional resection

Buchakjian et al. *Otolaryngol Head Neck Surg*. 2018; 159(4): 675-682.
Buchakjian et al. *JAMA Otolaryngol Head Neck Surg*. 2016. 142(12): 1191-1198.
Tasche et al. *JAMA Otolaryngol Head Neck Surg*. 2017. 143(12): 1166-1172.

Summary of studies on location for margin samples (defect vs specimen driven)

Yahalom et al prospective study: frozen section from resected tumor specimen best correlation with final margin status and patient survival

Chang et al retrospective study: no correlation between defect driven margin status and LR; positive specimen driven margin conferred relative risk of 2.5 for LR

Amit et al prospective randomized trial: permanent margin positivity rate 45% in defect driven arm, 16% in specimen driven arm; sensitivity: 91% vs 22% for specimen vs defect driven

Horwich et al combined retrospective and prospective: significant decrease in permanent margin positivity rate from 12.9% to 0.9% after switching from defect drive to specimen drive protocol

Varvares et al: retrospective study local recurrence rate 25% in defect driven vs 17.6% in specimen driven

Assessing margins from the resection specimen rather than the tumor bed consistently predicts local control

Amit et al. *Head & Neck*. 2016;38(S1).
Urken et al. *Oral Oncology*. 2023;143:106445.

Margin Distance

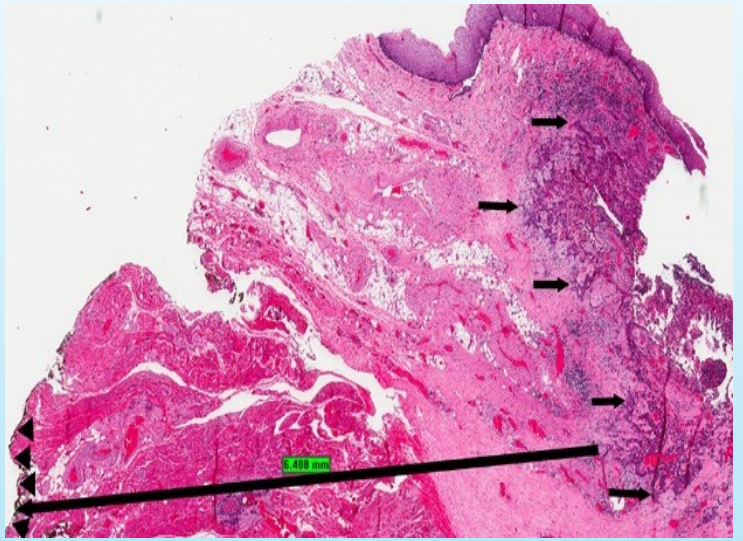
Baddour et al 2016

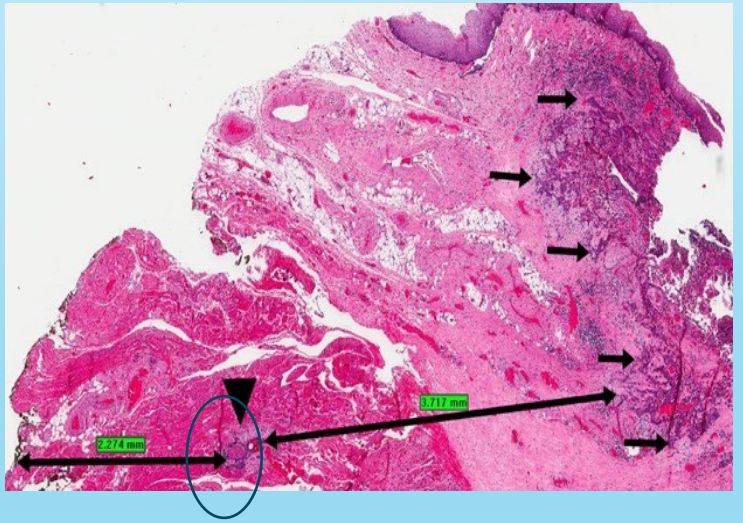
Margins in H&N cancer

Multiple definitions in literature on clear vs close vs positive margins

Largely retrospective data

Most data from oral cavity





NCCN:

Clear margin: > 5 mm from invasive tumor to resected margin

Close margin: 2-5 mm from invasive tumor to resected margin

Positive margin: carcinoma at resected margin

Caveat: adequate margin may vary by tumor type and site

RTOG 9501 randomized trial: positive margins = microscopic tumor infiltration at cut edge (<0.1 mm)

EORTC: positive margins – margin < 5 mm

Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.
Sunkara et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(4):317.
Hamman et al. *The Laryngoscope*. 2022;132(2):307-321.
Urken et al. *Oral Oncology*. 2023;143:106445.

Randomized trial: margin distance on survival

Secondary analysis multi-institutional randomized

688 pts stage III-IV resected SCC (oral cavity, OP, hypopharynx, larynx) with high risk features (ENE or +margins defined by EORTC)

Compared margin distance < 1 mm vs 1-5 mm for ENE-; < 1 mm vs 1-5 mm vs >5 mm for ENE+

ENE positive cohort:

- *65% risk of LRTF for > 5 mm margins vs < 1 mm margins (significant)*
- Patients with OC cancer → survival and time to LRTF improved for > 5-mm margins

No association between dysplasia in the surrounding tissue and OS for all patients

Sunkara et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(4):317

Systematic review

26 studies (8435 pts) → 96% oral cavity

Excluded transoral laser, robotic resections, previous treatment

Meta-analysis:

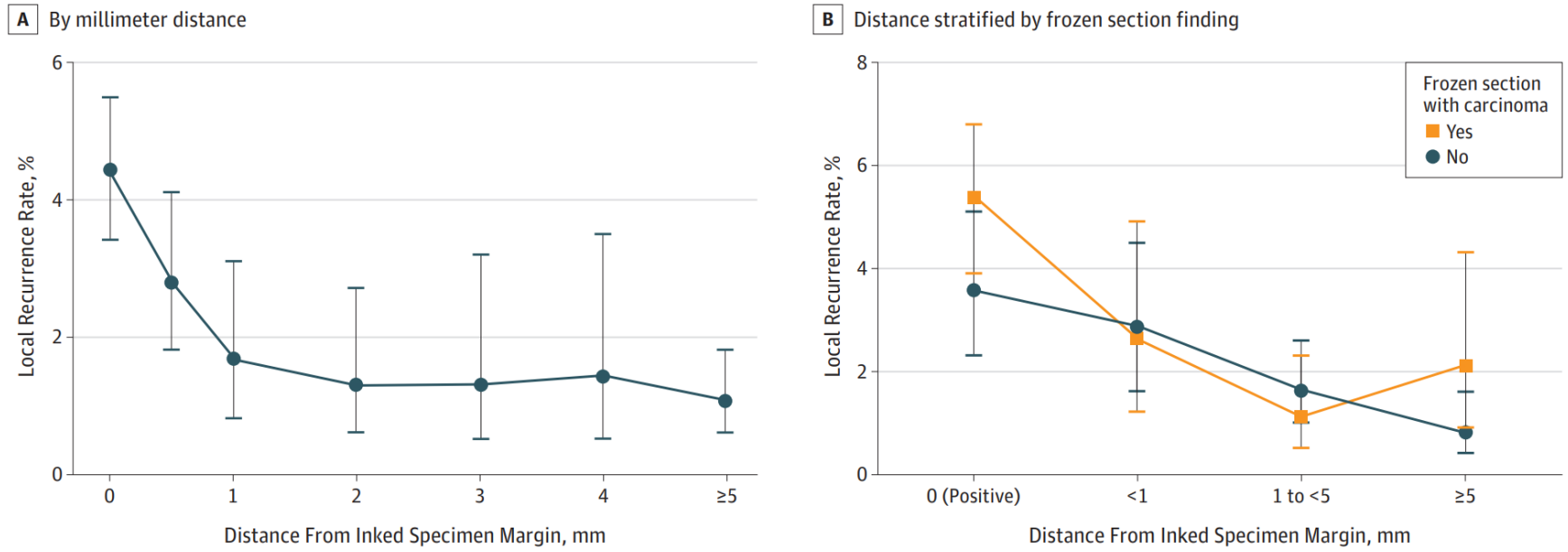
- *Clear margins significantly higher 5 yr OS and lower 5 yr LR compared to close margin*
- *Close margins lower incidence of 5 yr LR, no difference in 5 yr OS compared to involved margins*

	5 yr OS	5 yr LR
Clear margins	53.3-91.2%	5.2-27%
Close margins	37.5-70.1%	10.7-36%
Involved margins	29.8-85.1%	8.9-79.7%

Hamman et al. *The Laryngoscope*. 2022;132(2):307-321.

Tumor margins in oral cavity

Figure 1. Local Recurrence Rates by Specimen Margin Size (Distance From Invasive Cancer)



A, Local recurrence rate vs the distance from the cut specimen edge to invasive tumor in millimeters. B, Local recurrence rate vs the distance from the cut specimen edge to invasive tumor stratified by the intraoperative frozen section result.

Buchakjian et al: Close margin of < 1mm from invasive tumor associated with significantly increased risk of LR (28%)

Tasche et al. *JAMA Otolaryngol Head Neck Surg*. 2017. 143(12): 1166-1172.

“Close” margins

Retrospective review of 381 archived tumor specimens (primarily T1/2 oral cavity)

Optimal cutoff associated with local recurrence: 2.2 mm

- *Risk for local recurrence if margin 2.3-5 mm and > 5 mm not significantly different with adjustment for tumor size and adjuvant*
- *Higher recurrence rate if + margin or margin 0.01-2.2 mm compared to margin > 2.2 mm*

Multivariate model: margin status was variable most significantly associated with LRFS

- Positive margin 6x more likely to have local recurrence compared to margin > 2.2 mm
- Margin 0.01-2.2 mm was 2x more likely for local recurrence compared to margin > 2.2 mm

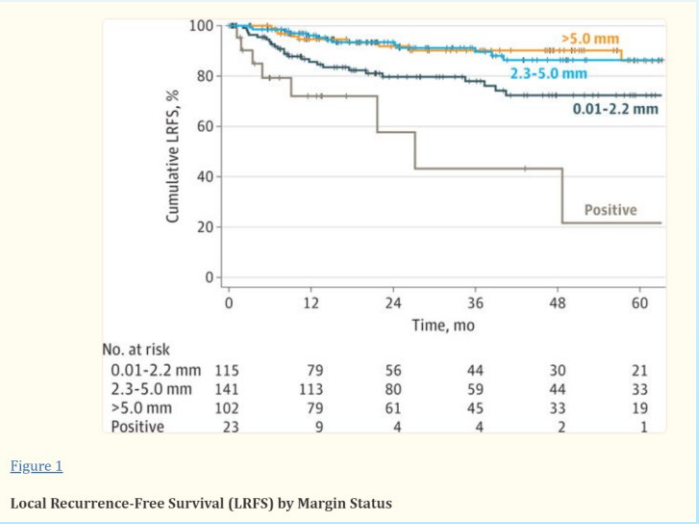


Figure 1

Local Recurrence-Free Survival (LRFS) by Margin Status

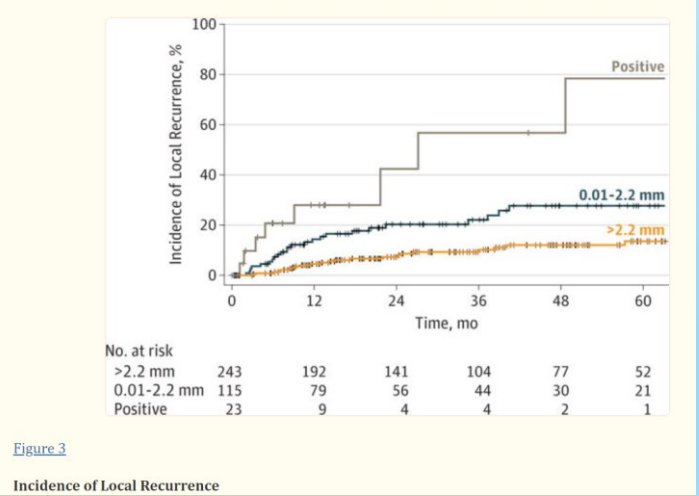


Figure 3

Incidence of Local Recurrence

Zanoni et al. *JAMA Otolaryngol Head Neck Surg*. 2017;143(6):555.

Clearing margins

Revising margins to negative margins → reduced local control compared to patients without history of transiently positive margins

Varvares et al: oral cavity SCC

- Higher local recurrence rate and worse DFS in patients resected to negative margins compared to patients with ≥5 mm margins and ≤5 mm but clear margins

Surrogate for more biologically aggressive disease

Revised margin inadequately cleared residual disease

Locating precise site of inadequate margin may be difficult

- Kerawala et al: re-locating site of margin revision has mean error of 9 mm for mucosal margins and 12 mm for deep margins (oropharynx primary)

Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.

Re-resection of margins in oral cavity

273 oral tongue cancers resected from 2013 to 2018

Additional resection performed if positive margin (invasive cancer/high grade dysplasia < 1 mm from inked edge)

- Negative margins vs positive margin with additional resection vs positive margin without additional resection

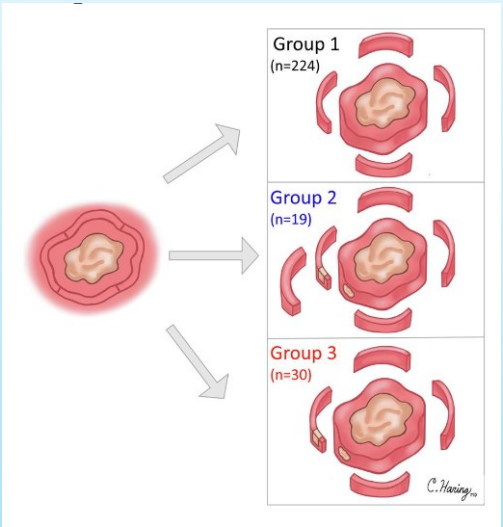
Margins from tumor bed

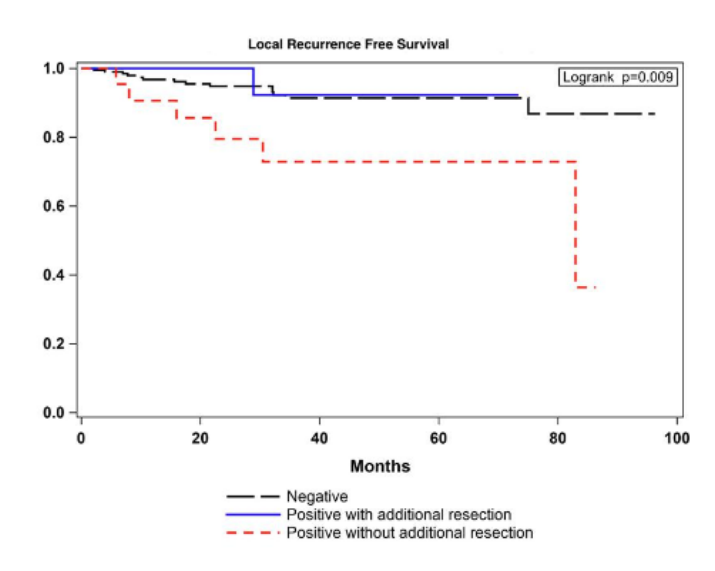
Local recurrence rate: 7.7%

Patients with +margin without additional resection → higher local recurrence

Patients with + margin with re-resection similar rate of recurrence as negative margin group

No difference in local recurrence free survival for patients with +margin with resection vs negative margins





Zhang et al. *Oral Oncology*. 2023;141:106402.

Positive vs negative margins

Loree and Strong: local recurrence 2x as common in patients with positive margins compared to negative margins (36 vs 16%)

Spiro et al: overall survival not affected by positive margin, revising initial positive margin to negative margin → not equivalent to initially negative margin on first resection

Scholl et al: patients with positive margins cleared to negative → worse local control and 5 yr OS compared to negative margins

- *Cleared positive margins benefitted from adjuvant therapy improving local recurrence rates to those with initially negative margins*

Puram et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(7):636.

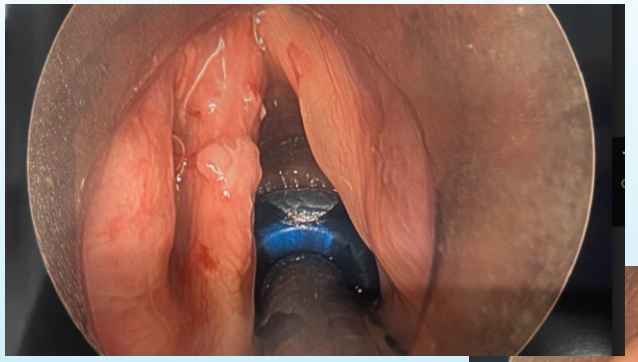
Margin impact on adjuvant treatment

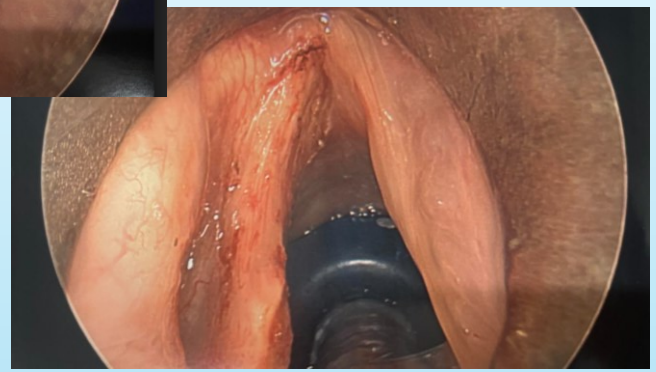
Positive margins (and ENE) adding chemotherapy to XRT:

- 42% reduction in locoregional failure

Baddour et al. *Journal of Surgical Oncology*. 2016;113(3):248-255.
Hinni et al. *Head Neck*. 2013;35(9):1362-1370.

Larynx





Concern: voice preservation with disease control

Often 1-2 mm margins considered adequate

Defect driven approach for margins typically

Reported as positive vs negative (rather than close)

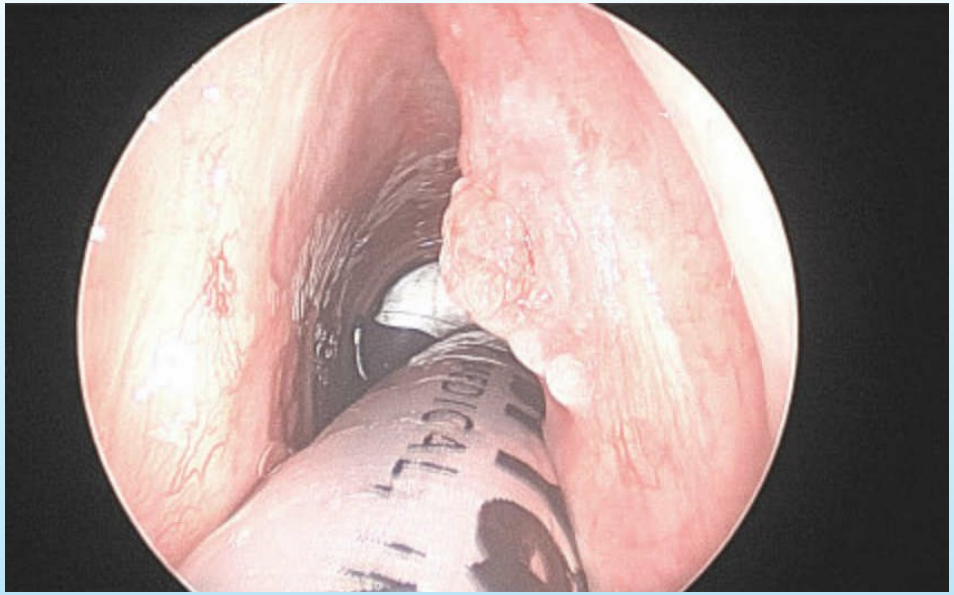
Studies (including higher stage glottic tumors) → worse local control with positive margins

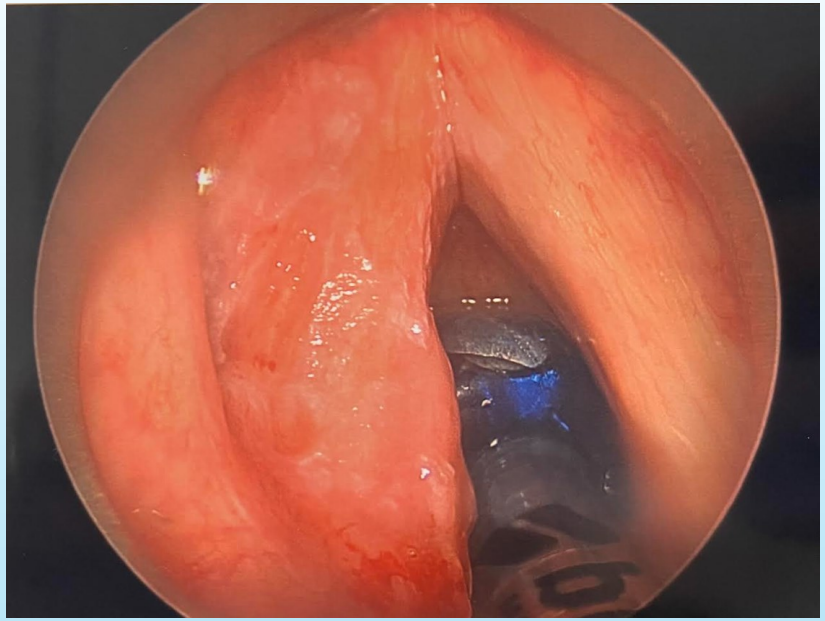
T1 glottic tumors → often transoral laser

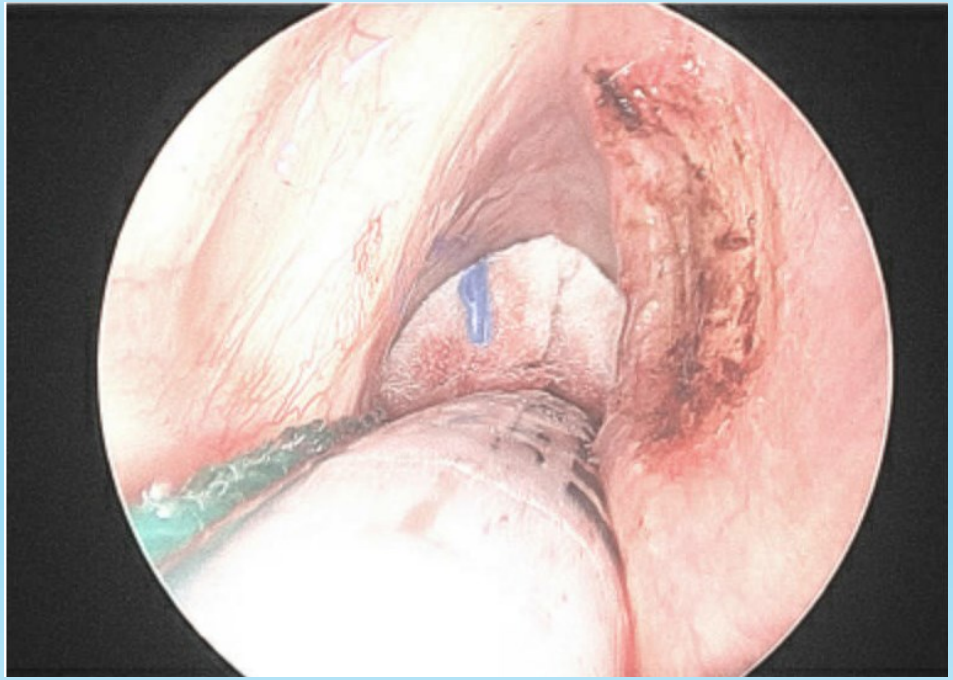
- *Close or positive margins no impact on local recurrence in retrospective studies*
- *Thermal laser effect on margin, overall good prognosis for T1 glottic, small size of specimen + shrinkage in workup*

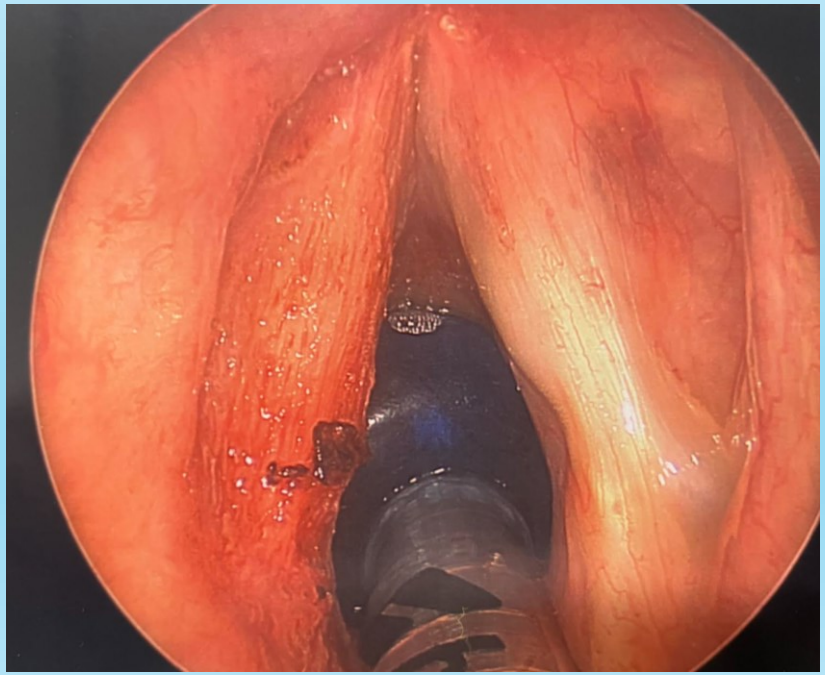
Often do a "second look" vs clinical follow-up → Retrospective studies show either valid

Hinni et al. *Head Neck*. 2013;35(9):1362-1370.
Li et al. *Ann Surg Oncol*. 2019;26(12):4070-4080.
Urken et al. *Oral Oncology*. 2023;143:106445.









Dysplasia

What about dysplasia

Typically clear high grade

Usually observe low grade

Severe dysplasia: risk of over/underdiagnosis due to subjective determination (Batsakis et al)

Field cancerization

Bulbul et al. *The Laryngoscope*. 2021;131(4):782-787.
Meier et al. *Head Neck*. 2005;27(11):952-958.
Gilvetti et al. *Oral Oncology*. 2021;121:105462.
Batsakis JG. *Advances in Anatomic Pathology*. 1999;6(3):140-148.

What about dysplasia

Dysplasia or CIS at margin → considered "positive" margin? (Meier et al)

Loree and Strong:

- Invasive carcinoma at margin or within 5 mm of margin, dysplasia at margin, CIS at margin all increase likelihood of local recurrence
- 5 yr survival rates: 94% with dysplasia, 71% with CIS, 51% with close margin, 43% with invasive carcinoma at margin

Batsakis et al: CIS and dysplasia have equal biologic significance

WHO: malignant transformation rate (Gilvetti et al):

- Mild → 6%
- Moderate → 18%
- Severe/CIS → 39%

Bulbul et al. *The Laryngoscope*. 2021;131(4):782-787.
Meier et al. *Head Neck*. 2005;27(11):952-958.
Gilvetti et al. *Oral Oncology*. 2021;121:105462.
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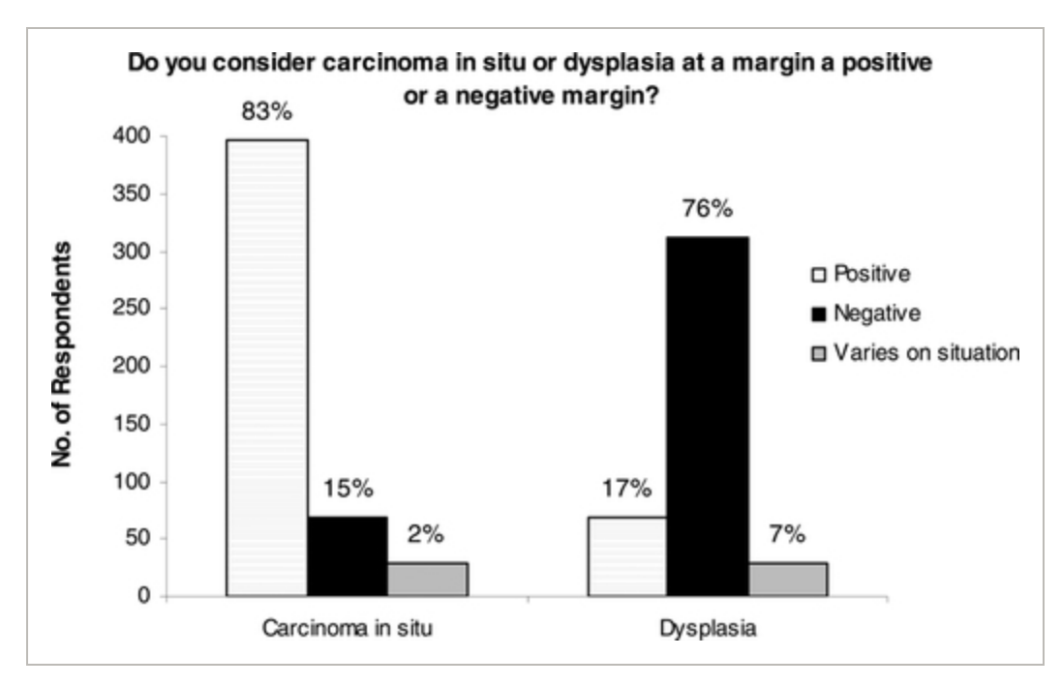
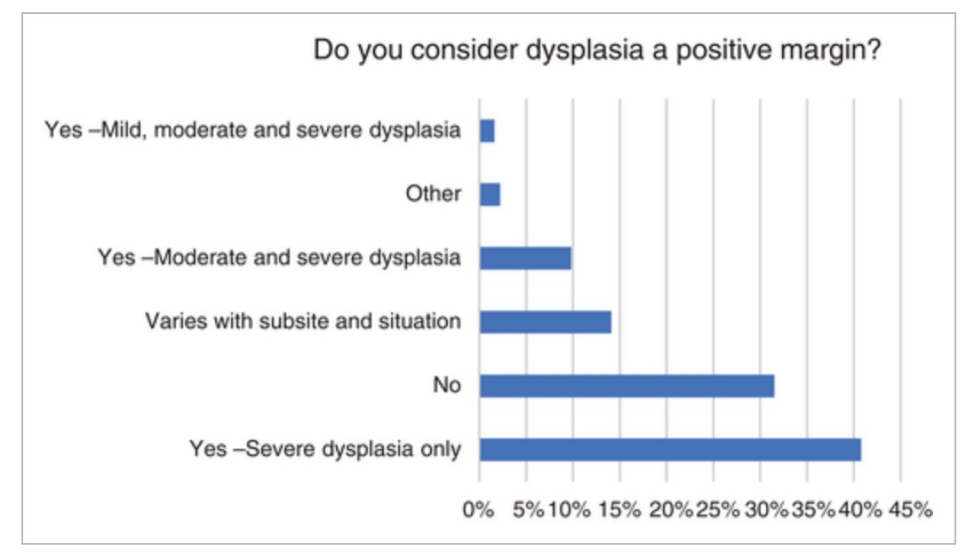
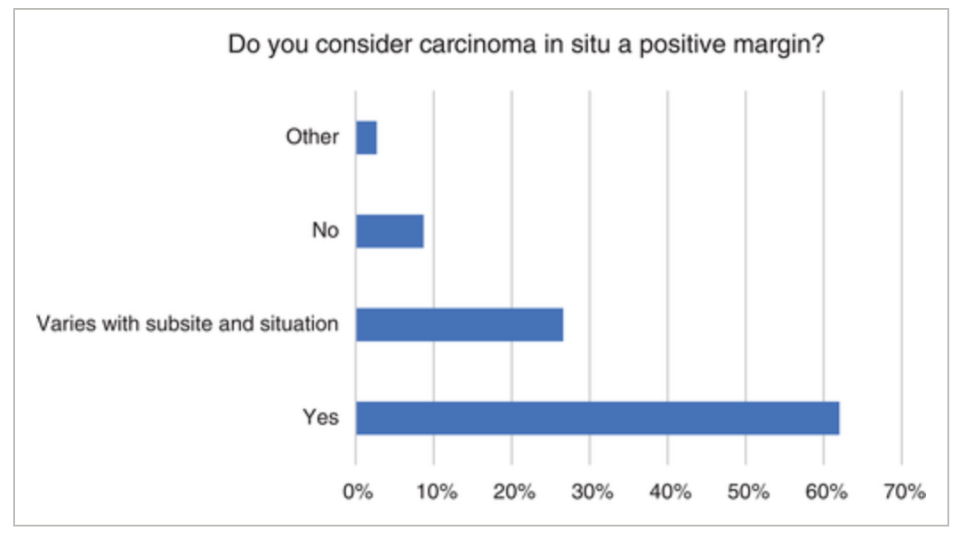
Dysplasia management: AHNS Surgeon Perspective







Bulbul et al. *The Laryngoscope*. 2021;131(4):782-787.
Meier et al. *Head Neck*. 2005;27(11):952-958.

Dysplasia conversion

Systematic review with meta-analysis (Mehanna et al 2009)

- 14 studies (prospective/retrospective) with 992 patients
- 12.3% rate of transformation to cancer (higher for severe dysplasia/CIS)
- Surgical excision decrease risk of transformation (14.6% vs 5.4%)
- Mean time to transformation: 4.3 yrs

UK 10 yr clinical study (Gilvetti et al 2021)

- High grade dysplasia treated with excision – 120 pts, mean f/u 47.7 months
- 18.3% excisions → SCC
- 33 pts (34.7%) → subsequent recurrent high grade dysplasia at same site, mean time 62 months (22-144 mo)
- 17 (17.8%) → SCC at same site, mean time transformation 50 months (8-97 mo)
- 4/14 pts (28.6%) without resection → SCC vs 13/106 pts (12.3%) who treated with surgery
- Malignant transformation associated with age, site, treatment, positive excision margins

Gilvetti et al. *Oral Oncology*. 2021;121:105462.
Mehanna et al. *Head Neck*. 2009;31(12):1600-1609.

False negative frozen section

False negative frozen section

Permanent correlation rate of 96-99%

Often sampling error (vs interpretation error)

Carcinoma absent in frozen section slide, present in permanent after deeper cuts in formalin fixed paraffin embedded block

Recommend multiple levels at time of frozen section decrease false negatives

- Study at large academic center: (4976 frozens)
  - *Overall error rate: 2.4% for 2 levels vs 2.5% for 3 levels (p=0.67)*
  - *Sampling error rate: 1.6% for 2 levels vs 1.2% for 3 levels (P=0.42)*
  - *Only frozen sections where tumor identified sampling error rate: 15.3% for 2 level vs 7.4% for 3 level (P=0.006)*
- Conclusion: single additional deeper level for frozen section identifies more tumor bearing specimens, may reduce sampling errors

University of Minnesota: 3 levels routinely, University of Iowa: tissue exhausted

False negatives: treatment, financial, functional implications for patients (vs cost of additional slide/time)

Hinni et al. *Head Neck*. 2013;35(9):1362-1370.
Olson et al. *Modern Pathology*. 2011;24(5):665-670.
Cooley et al. *Head Neck*. 2002;24(3):262-267.
Meier et al. *Head Neck*. 2005;27(11):952-958.

Frozen section discrepancy rates

Sampling

Gross sampling: initial gross examination of specimen –> tumor not selected for frozen but present in sections submitted for permanent

Block sampling: lesion selected and included in block but levels of tissue examined for frozen shown as no tumor and instead detected on permanent section done on remaining tissue

Technical

Poor freezing, cutting or staining techniques, tissue loss during processing, mislabeling of slides

Interpretative

Findings present on frozen section but misdiagnosed by pathologist

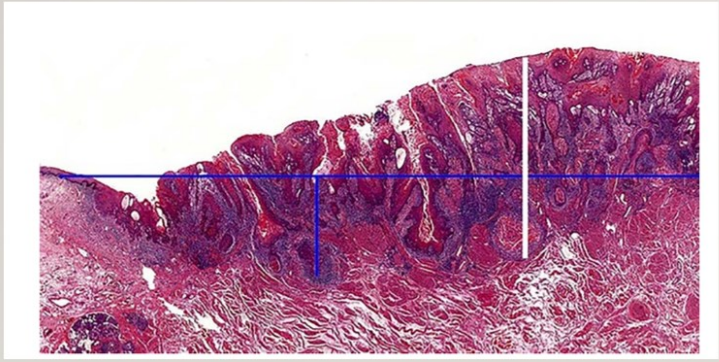
As many as 22.1% of all cases with intraoperative frozen sections interpreted as negative may have a close or positive margin on analysis of the main specimen, implying sampling error (Li et al)

Serinelli et al. *Head and Neck Pathol*. 2022;16(2):466-475.
Li et al. *Ann Surg Oncol*. 2019;26(12):4070-4080.

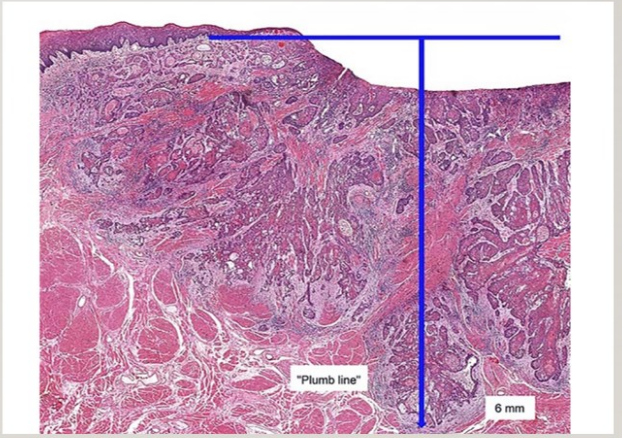
Tongue depth of invasion

Tongue cancers – depth of invasion

TUMOR THICKNESS (WHITE) > DOI (BLUE)



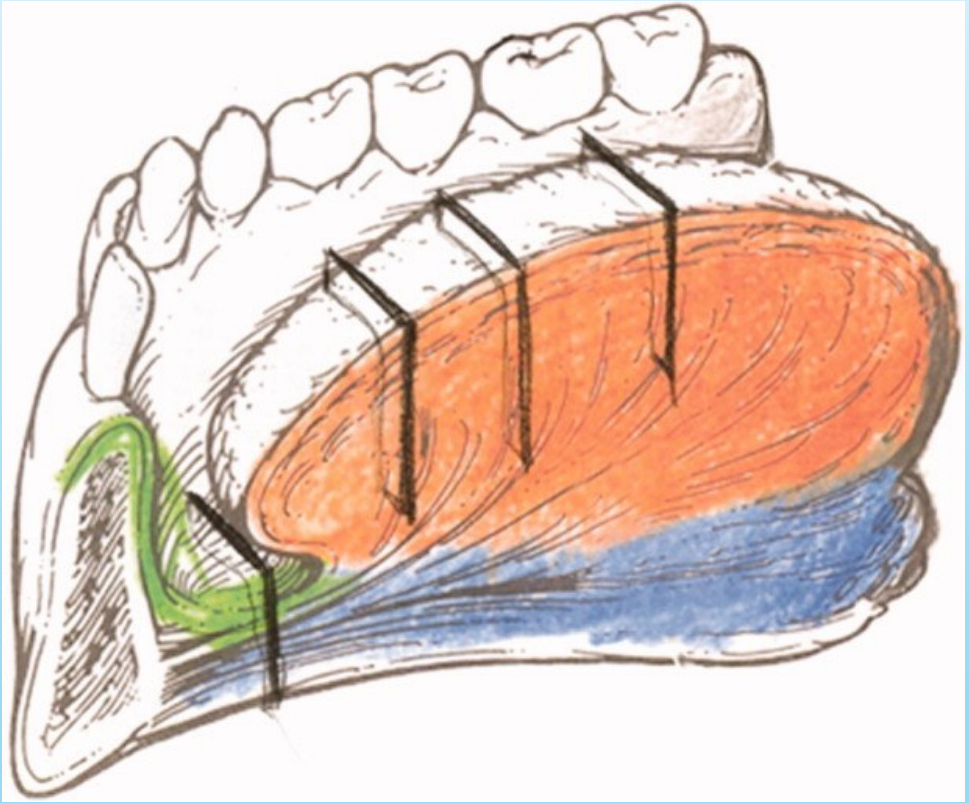
TUMOR THICKNESS <DOI (EX ULCERATED TUMOR)



Lydiatt et al. *CA Cancer J Clin*. 2017. 67(2): 122-137.

DOI

Perpendicular cuts into specimen



Hinni et al. *Head Neck*. 2013;35(9):1362-1370.

Oral cavity elective neck

Enrollment stopped due to elective neck superiority

Untreated T1-2 SCC oral cavity, elective vs therapeutic neck

3 years: OS 80.0% vs 67.5%

Tumor grade, PNI, LVSI, DOI associated with OS

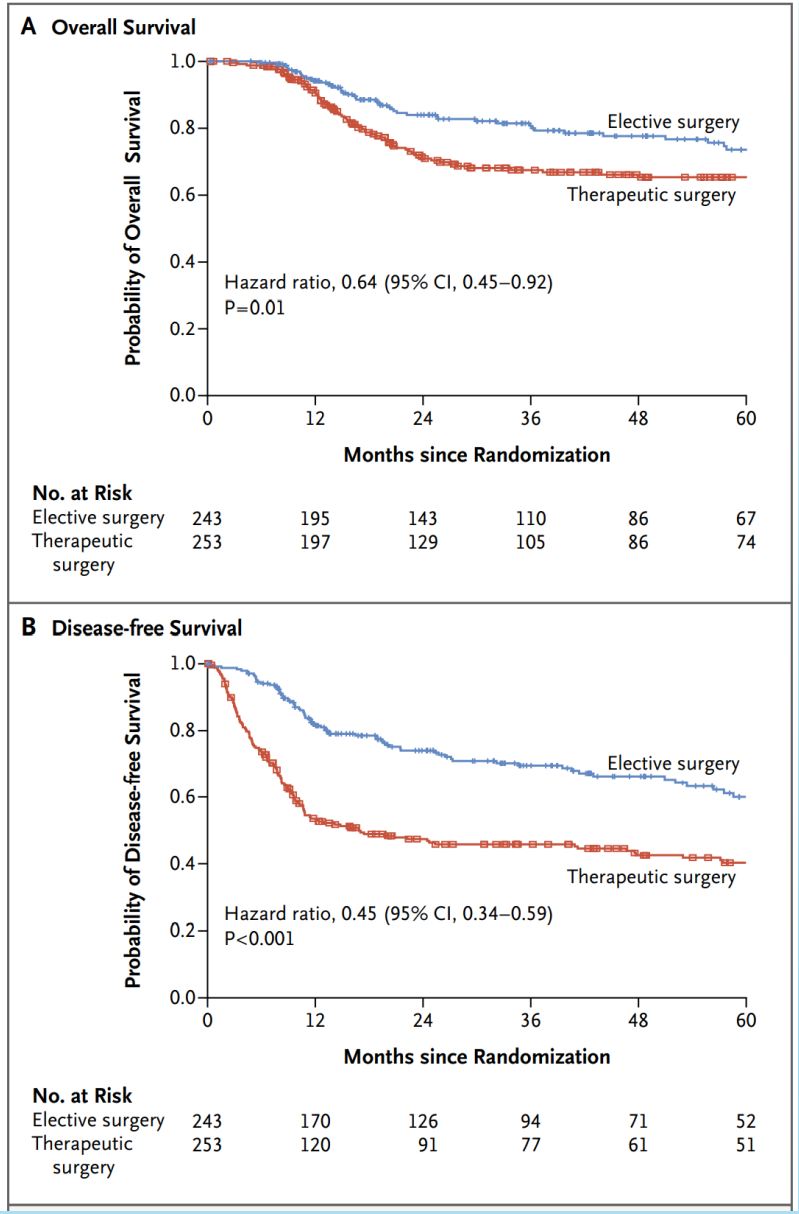
3 years: DFS 69.5% vs 45.9%

Lack of benefit of elective neck DOI < 3 mm

Node positivity: DOI 3 mm → 5.6%, DOI 4 mm → 16.9%

Nodal relapse: more advanced nodal stage, higher rate ENE

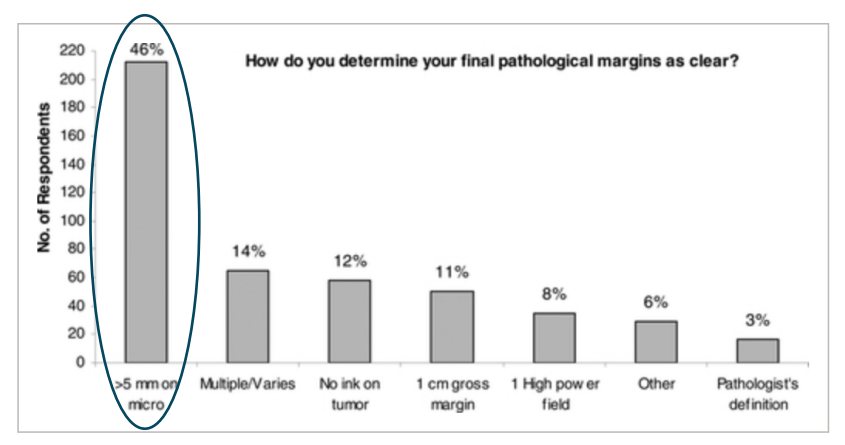
- 8 pts need to be treated with elective neck to prevent 1 death
- 4 pts need to be treated to prevent 1 relapse

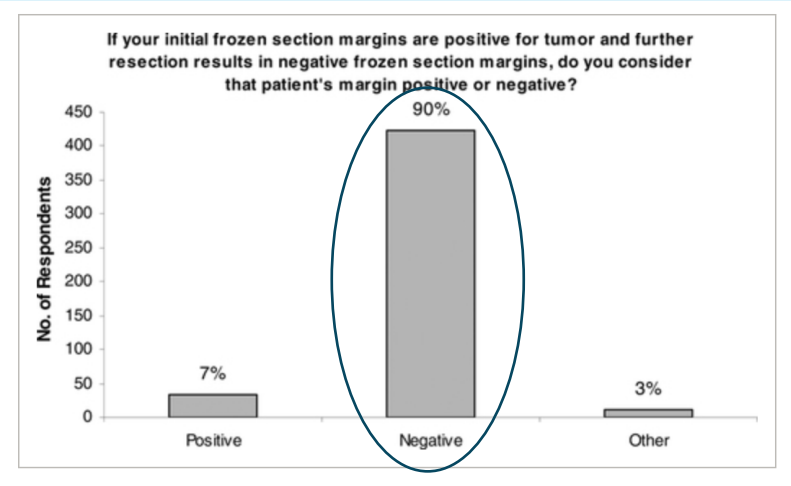


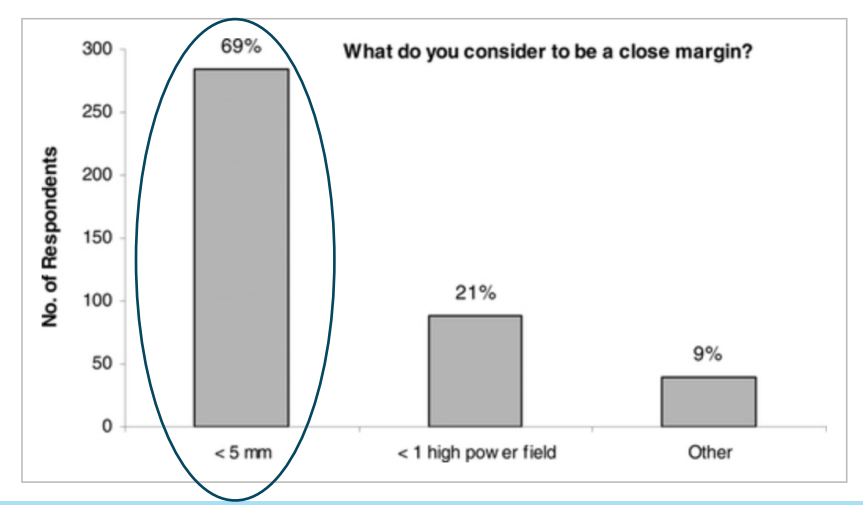
D'Cruz et al. *N Engl J Med*. 2015; 373(6):521-9.

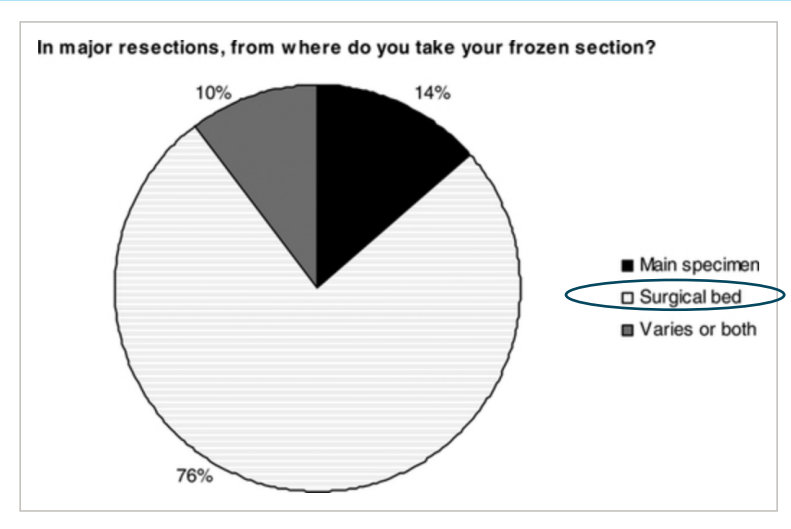
H&N Surgeon Practice

H&N surgeon perspective (2005): 476 AHNS respondents







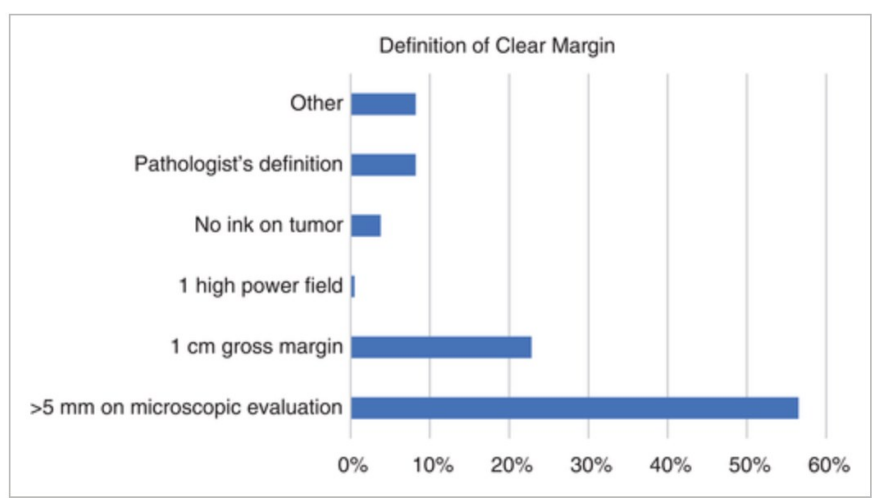


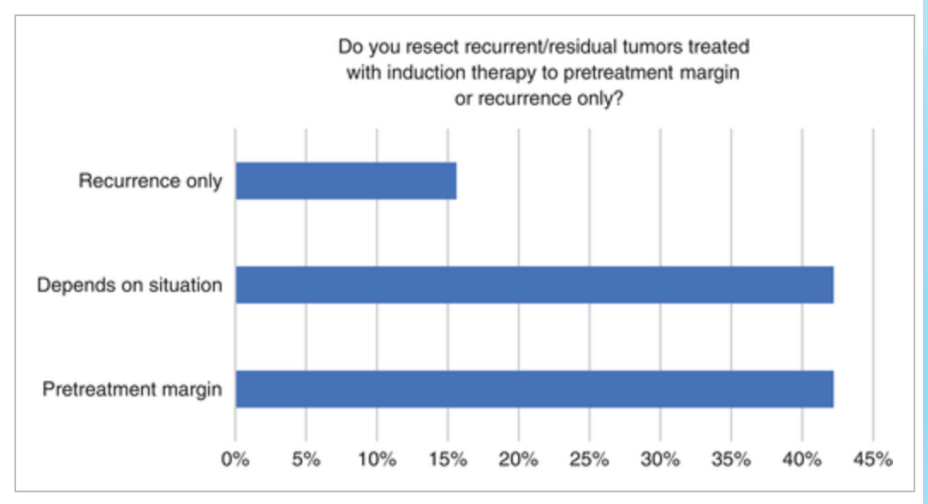
Meier et al. *Head Neck*. 2005;27(11):952-958.

H&N surgeon perspective (2019): 185 AHNS respondents

55% (98) take frozen from main specimen vs 45% from tumor bed

- Specimen based reason: 75.5% cited evidence in the literature and 58.2% cited reduced sampling error as reasons for choice
- Tumor bed reason: 37.5% less sampling error, 31.25% more convenient; other avoid margins look artificially close, avoid disruption of main specimen for lateral pathology analysis





Bulbul et al. *The Laryngoscope*. 2021;131(4):782-787.

AHNS review: stage I and II oral cavity

Gross specimen must be accurately oriented

Direct communication between surgeon and pathologist ideal compared to anatomic landmarks or orienting sutures alone

Close or positive margins should be communicated in terms of millimeter of radial distance with reference to identifiable anatomic landmarks

- "Negative" margin has to mean a specific *minimum radial distance clearance*
- Specimens should *be obtained perpendicular to surgical margin by cutting toward or into tumor after inking true margin*

Nonmargin cuts or tears should be communicated/oriented/marked

- *Oncologic implications unclear*
- *Ink these areas with unique color to distinguish from true resection margin*

Surgeons should anticipate tissue shrinkage when planning gross margin

- *Goal of final 5 mm margin, should remove 10-15 mm of surrounding mucosa*

Deep margin assessment: ink entire deep surface of specimen then cut perpendicular to specimen in area closest by palpation

Puram et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(7):636.

AHNS review: stage I-II oral cavity margins

Recommendations:

- Aim for gross margin of 10-15 mm to reduce risk of close or positive margin
- Obtaining negative margin resection on first attempt crucial to minimize risk of local recurrence
- Revision to negative margin from initially positive margin not equivalent to initially negative margin but despite high level evidence recommend re-resection to clear margin

Puram et al. *JAMA Otolaryngol Head Neck Surg*. 2023;149(7):636.

Take home points

- Surgical tumor margins have direct impacts on local recurrence and survival for oral cavity cancers.
- Surgical margins from the specimen have better association with outcomes than tumor bed driven specimens
- Direct communication with the pathology team allows for correct orientation and accurate reflection of specimen margins
- Depth of invasion for tongue cancers rather than tumor thickness dictates need for elective neck dissection, with implications on overall and disease free survival.

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