1

Faculty Disclosures

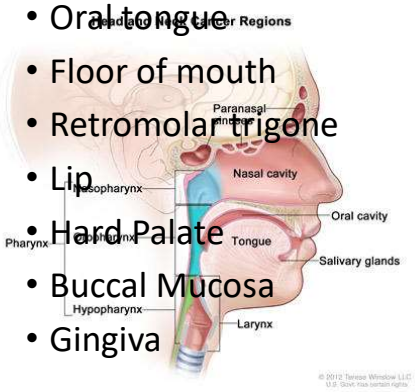
- Dr. Lai is the PI for NRG-HN006 and a Medical Affairs consultant with Cardinal Health.

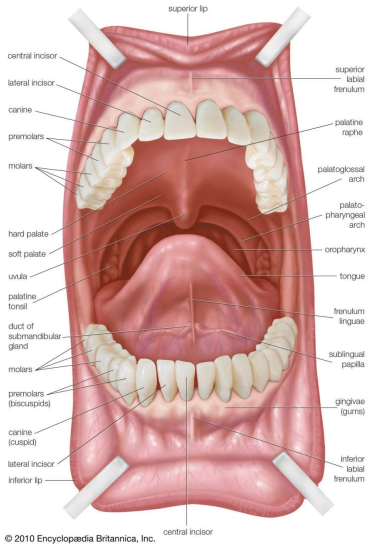
- Research support and effort:
  - R01 DE025248
  - R01 CA280980
  - R01 DE028290
  - R21 CA259839
  - T32 CA261856
  - U54 CA274321 (Project 3)

2

Anatomic Subsites of the Oral Cavity

- Oral tongue
- Floor of mouth
- Retromolar trigone
- Lip
- Hard Palate
- Buccal Mucosa
- Gingiva





3

Case Study: Oral Cavity Cancer

Physical Exam

Size

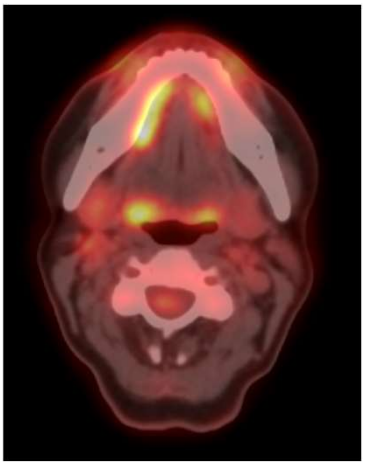
Exophytic/Endophytic

Location
- Subsite(s)
- Adjacent structure involvement

Movement

4

Pre-operative Imaging Evaluation



CT

MRI

PET/CT

US-guided FNA Bx

5

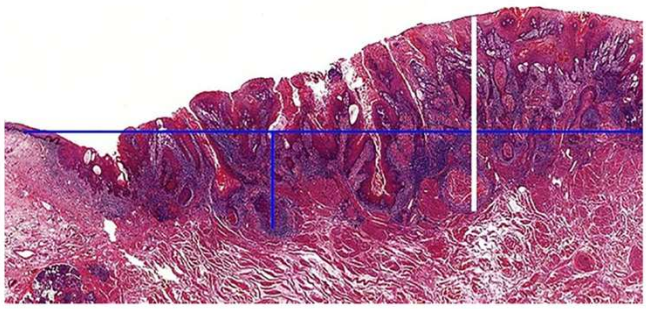
Clinical Staging - Tumor AJCC (8th edition)

TABLE 9. T Category for Oral Cavity Cancer, 8th Edition Staging Manual[a]

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm, ≤5 mm depth of invasion (DOI) (DOI is depth of invasion and not tumor thickness)
T2	Tumor ≤2 cm, DOI >5 mm and ≤10 mm *or* tumor >2 cm but ≤4 cm, and ≤10 mm DOI
T3	Tumor >4 cm *or* any tumor >10 mm DOI
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease: (lip) tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose); (oral cavity) tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face); note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery

[a]Table 9 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]).

Tumor thickness ≠ Depth of Invasion



Lydiatt et al., *CA Cancer J Clin*, 2017

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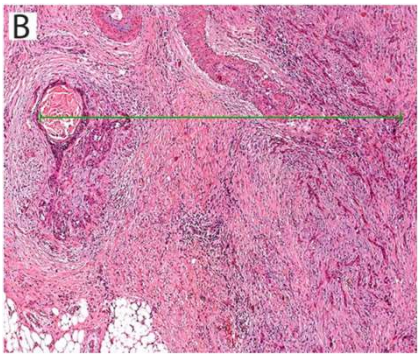
Clinical Staging – Lymph Node AJCC (8th edition)

TABLE 10. Regional Lymph Nodes Pathologic Category Criteria (pN)[a]

N CATEGORY	N CRITERIA[b]
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-negative
N2	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE-positive; *or* more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative; or metastases in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative; *or* metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension, ENE-negative
N2a	Metastasis in a single ipsilateral or contralateral lymph node 3 cm or less in greatest dimension and ENE-positive; *or* metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative; or metastasis in a single ipsilateral lymph node more than 3 cm in greatest dimension and ENE-positive; *or* metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a	Metastasis in a lymph node more than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in a single ipsilateral node more than 3 cm in greatest dimension and ENE-positive; *or* metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive

Abbreviations: ENE, extranodal extension. [a]Table 10 is used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC (springer.com) (Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, with permission[2]). [b]Note that a designation of "U" or "L" may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as ENE-negative or ENE-positive.

Extranodal Extension (ENE)



Lydiatt et al., *CA Cancer J Clin*, 2017

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Clinical Staging – Early v Late Stage Disease AJCC (8th edition)

Cancer Stage	T Category	N Category	M Category
0	Tis	No	Mo
I	T1	No	Mo
II	T2	No	Mo
III	T1, T2 T3	N1 No, N1	Mo Mo
IVA	T1, T2, T3 T4a	N2 No, N1, N2	Mo Mo
IVB	Any T4b	N3 Any	Mo Mo
IVC	Any	Any	M1

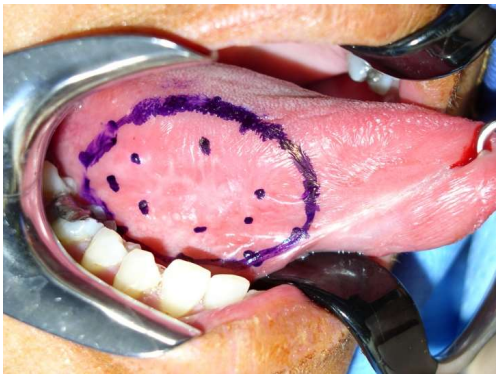
	N CATEGORY			
T CATEGORY	N0	N1	N2a,b,c	N3a,b
T1	I	III	IVA	IVB
T2	II	III	IVA	IVB
T3	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVB
T4b	IVB	IVB	IVB	IVB

[a]Any M1 is stage IVC.

Lydiatt et al., *CA Cancer J Clin*, 2017

8

Case Study: Oral Cavity Cancer



Resection of the primary tumor with >5 mm negative margins on **<u>final</u>** pathological analysis

9

Positive Surgical Margins in the 10 Most Common Solid Tumors

	BREAST (LUMP, MAST, TOTAL)			PROSTATE	BLADDER	COLON & RECTUM	THYROID	ORAL CAVITY	LUNG & BRONCHUS	KIDNEY & RENAL PELVIS	UTERINE	OVARIAN	TOTAL
Number of Cases (n)	1,479,230	1,051,335	2,530,565	761,637	241,791	1,218,834	314,459	120,826	462,482	361,240	391,997	92,058	6,495,889
Number of PSM Cases	97,335	55,746	153,081	160,194	23,317	83,241	36,230	15,411	33,861	20,691	16,938	32,217	575,181
Overall PSM Rate (%)	6.58	5.30	6.05	21.03	9.64	6.83	11.52	12.75	7.32	5.73	4.32	35.00	8.85%

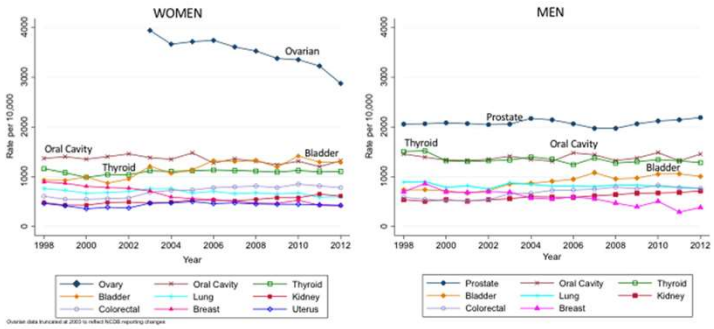


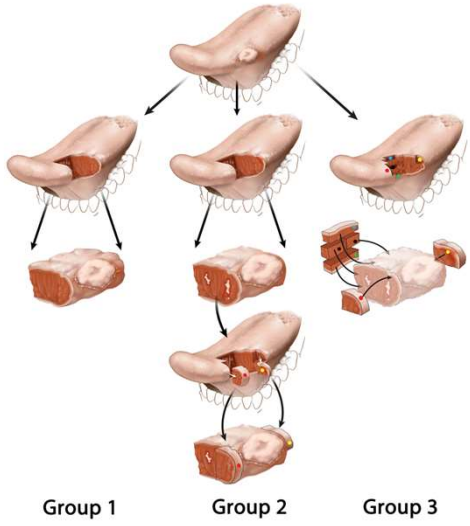
Figure 1. Positive surgical margin (PSM) prevalence (reported as rate per 10,000 patients) for each cancer in women (**A**) and men (**B**) as a function of time.

Orosco et al. Sci Reports 2018

10

Sampling method for intra-operative frozen: bed vs specimen

- Multi-institutional retrospective study T1-2N0 tongue SCC (n=280)
  - **Group 1**: no bed margins sampled, all margins from specimen – 7.7% positive
    Group 2: margins from specimen and re-resect if suboptimal or positive – 45.9% positive margins
  - **Group 3**: margins sampled from bed without examining specimen – 24.5% positive margins (but frozen only positive 7.4%)
- Status of margins from specimen correlated with LR, bed did not – bed sampling only 24% sensitive

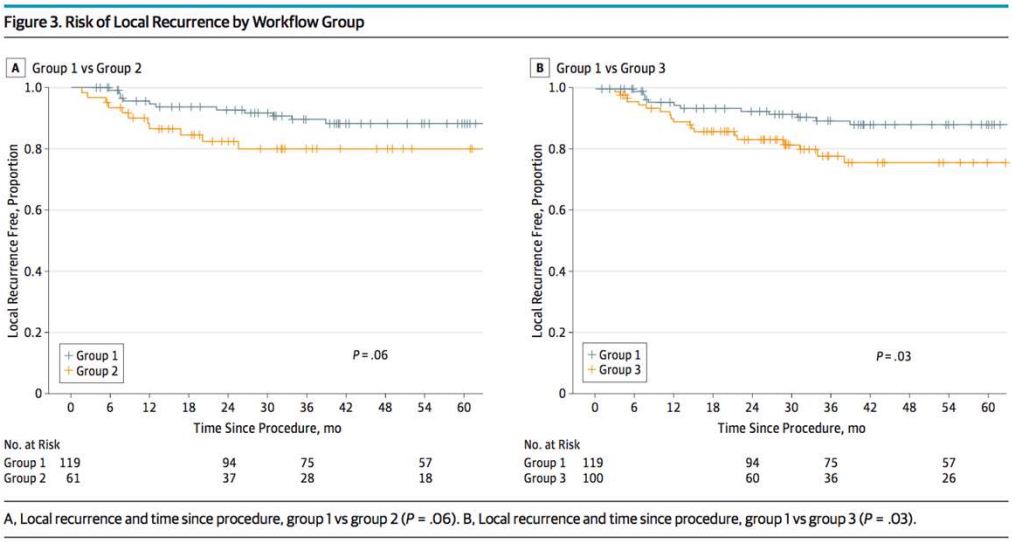


Maxwell et al., *JAMA Otolaryngol-Head and Neck Surg*, 2015

(courtesy M Vavares)

11

Sampling method for intra-operative frozen: bed vs specimen



Maxwell et al., *JAMA Otolaryngol-Head and Neck Surg*, 2015

(courtesy M Vavares)

12

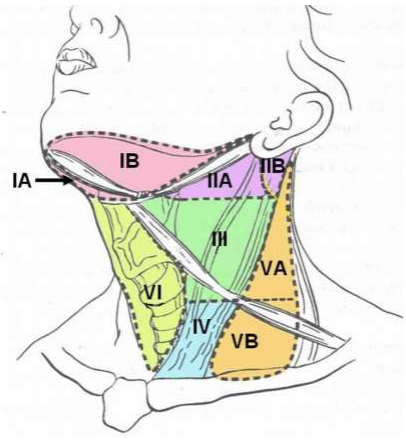
Points for Consideration

- Resection of the primary tumor with >5 mm negative margins on **final** pathological analysis.
- Consider margin assessment from the resection specimen by the **pathologist** rather than surgeon directed margin determination from the tumor specimen or resection bed.
- Re-resection of the close/positive surgery margin is permitted.
- Negative surgical margins are associated with survival.

13

Lymph Node Drainage: Oral Cavity Cancers

- Defined by level within the neck (cervical) nodes and differs by primary tumor site
- Oral cavity cancers primarily drain to **Levels IA and IB, II, and III - *(IV "skip" metastases)***
- The risk of metastases to lymph nodes is increased by high-grade histology and larger lesion size
- Sites close to the midline often drain bilaterally
- **N+ disease should be addressed with a comprehensive neck dissection**
- **T3-4 N0 should have at least a supraomohyoid neck dissection**



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How Do We Treat the Neck?

Early-stage oral cavity cancer (T1-2N0)

Observation "Watchful Waiting"

Sentinel Lymph Node Biopsy

Elective Neck Dissection

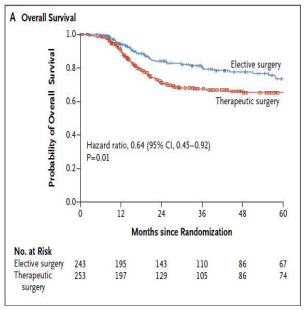
15

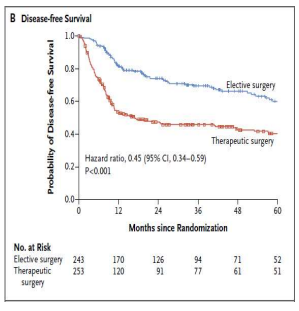
Elective vs Therapeutic Neck Dissection for Node-Negative Oral Cancer

- Randomized, prospective design
- 500 pts; T1/2 N0 previously untreated SCCa; (exclude upper alveolus/palate)
- 85.3% oral tongue primary lesion

	WW-TND	END
Nodal Recurrence	74%	31%*
3yr DFS	45.9%	69.5%*
3 yr OS	67.5	80.0%*

*greater % END receive XRT





D'Cruz et al NEJM, 2015

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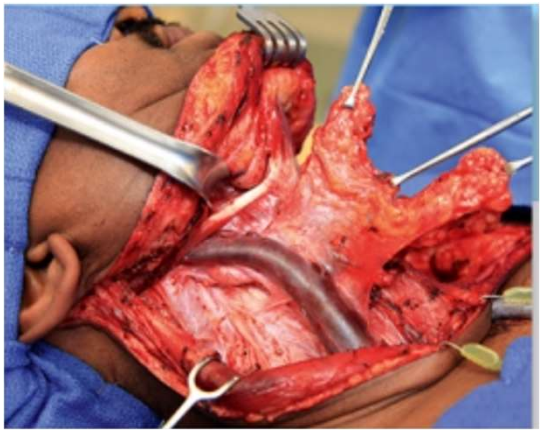
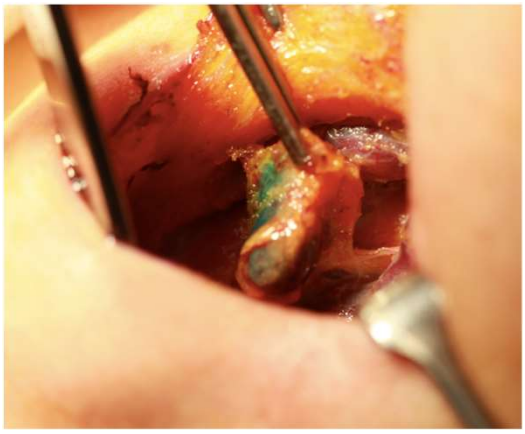
Management of "At Risk" Cervical Lymph Nodes



Elective Neck Dissection



Sentinel Lymph Node Biopsy

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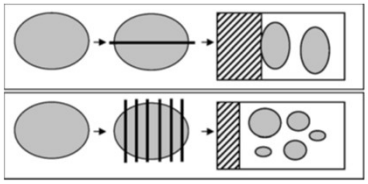
SLNB vs END: Potential Advantages

- **Focuses pathologic analysis on nodes most likely to harbor disease**



- **May potentially decrease surgical morbidity**
- **Accounts for unexpected patterns of lymphatic drainage**

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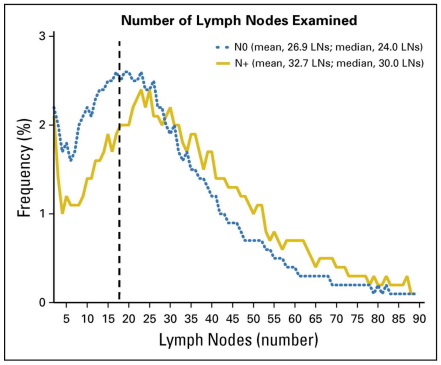
Elective Neck Dissection

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Lymph Node Count From Neck Dissection Predicts Mortality in Head and Neck Cancer

Vasu Divi, Michelle M. Chen, Brian Nussenbaum, Kim F. Rhoads, David B. Sirjani, F. Christopher Holsinger, Jennifer L. Shah, and Wendy Hara

≥18 nodes



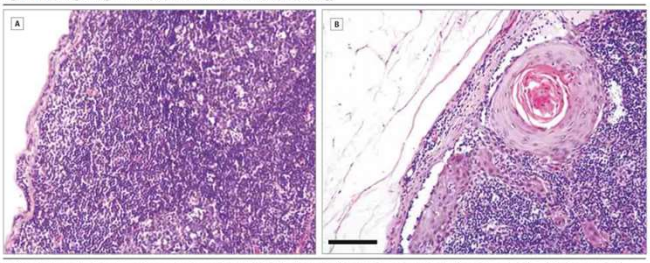
Divi et al. JCO 2016

The Origin of Regional Failure in Oral Cavity Squamous Cell Carcinoma With Pathologically Negative Neck Metastases

Moran Amit, MD, MSc; Tzu Chen Yen, MD, PhD; Chun Ta Liao, MD; Pankaj Chaturvedi, MD; Jai Prakash Agarwal, MD; Luiz Paulo Kowalski, MD, PhD; Hugo F. Kohler, MD; Ardalan Ebrahimi, MBBS; Jonathan R. Clark, MBBS; Claudio Roberto Cernea, MD, PhD; Jose S. Brandao, MD; Matthias Kreppel, MD, PhD; Joachim E. Zöller, MD; Leonor Leider-Trejo, MD; Gideon Bachar, MD; Thomas Shpitzer, MD; Andrea Villaret Bolzoni, MD; Raj P. Patel, MD; Sashikanth Jonnalagadda, MD; Thomas Kevin Robbins, MD; Jatin P. Shah, MD; Snehal G. Patel, MD; Ziv Gil, MD, PhD

15% FNR

Figure 1. Pathologic Images From a Representative Case of Revised Pathology



A, Pathologic sample originally read as negative for metastasis. B, Pathologic sample after resectioning prompted a change in reading to positive for metastasis. Original magnification ×20 and hematoxylin-eosin stain for both panels.

Amit et al. JAMA Oto-HNS 2014

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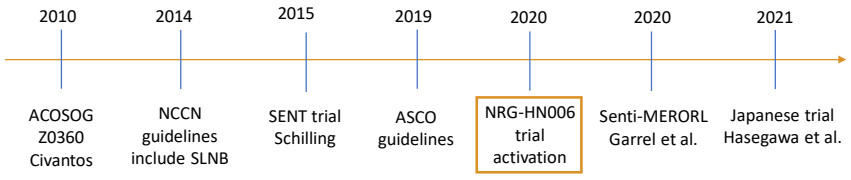
Timeline for Changing Clinical Practice[1,2]



- NCCN guidelines are updated to include SLNB as a recommendation
- Latest version of ASCO guidelines (2019) doesn't recommend SLNB for OCC – citing a more definitive study is required…however there is recognition that SLNB may become the standard of care
- **The goal of NRG-HN006 is to be the DEFINITIVE study that shows SLNB is non-inferior to END** (5% disease free survival non-inferiority margin)

1 Guidelines Detail (nccn.org)
2 Head and Neck Cancer | ASCO

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Multicenter Trial of [18F]fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the NO Neck: Results From ACRIN 6685

Val J. Lowe, MD[1]; Fenghai Duan, PhD[2]; Rathan M. Subramaniam, MD, PhD, MPH[3]; JoRean D. Sicks, MS[2]; Justin Romanoff, MA[2]; Twyla Bartel, DO[4]; Jian Q. (Michael) Yu, MD[5]; Brian Nussenbaum, MD, MHCM[6]; Jeremy Richmon, MD[7]; Charles D. Arnold, MD[8]; David Cognetti, MD[9]; and Brendan C. Stack Jr, MD[10]

TABLE 2. Results of the FDG-PET/CT Imaging and Pathology

NO Sides of Necks With Pathology Results	Pathology, No. Negative	Positive	Total
Best available FDG-PET/CT			
Negative	125	19	144
Positive	70	56	126
Total	195	75	270
Head and neck FDG-PET/CT			
Negative	106	16	122
Positive	65	47	112
Total	171	63	234

Abbreviations: CT, computed tomography; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography.

- T2-4 lesions
- NPV 0.868 (95% CI, 0.803 to 0.925)
- Concern related to FPR

Negative PET/CT has not been validated as a method for deciding on need for a neck dissection

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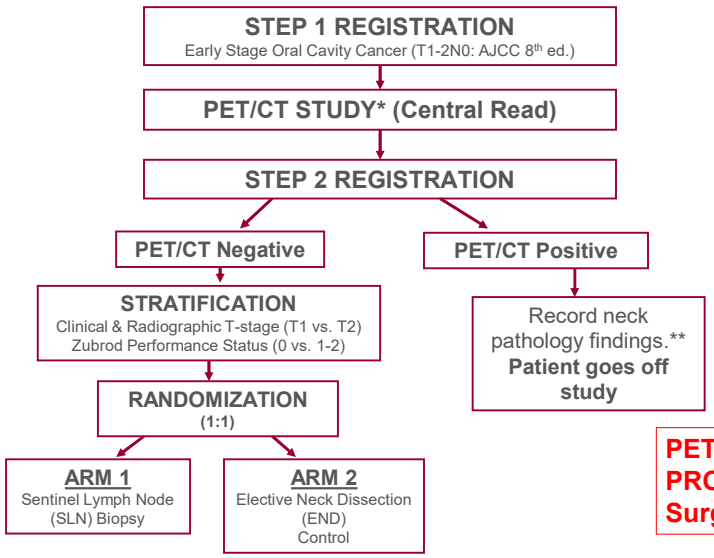
Study Schema



PET/CT (central review)
PRO (NDII)
Surgeon Credentialing

NRG ONCOLOGY™

** See Protocol Section 3.1 for details*
*** See Protocol Section 8.3 for details*

NRG-HN006

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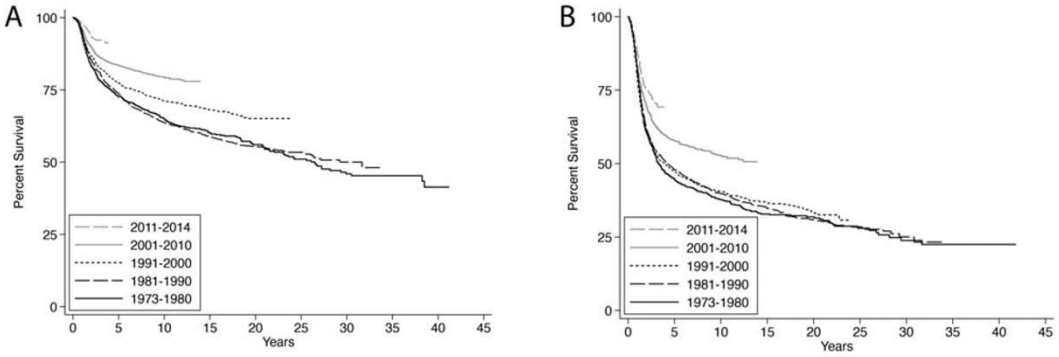
Oral Cavity Cancer Prognosis: Early- and Late-Stage Disease



Early-Stage Disease

Late-Stage Disease

Cheraglou et al., *CA Cancer J Clin*, 2017

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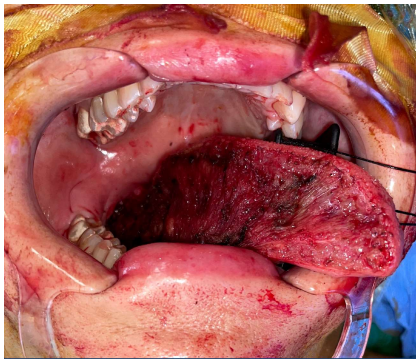
Case Study: Oral Cavity Cancer



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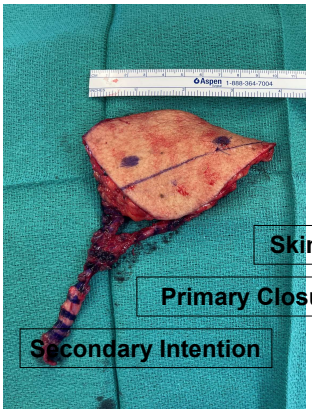
Case Study: Oral Cavity Cancer



Secondary Intention

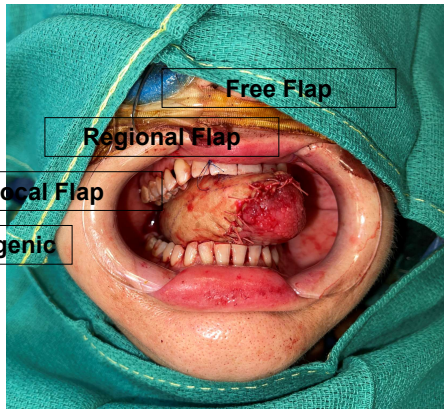
Primary Closure

Skin Graft/Allogenic

Local Flap

Regional Flap

Free Flap



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AMERICAN ACADEMY OF OTOLARYNGOLOGY-HEAD AND NECK SURGERY

Sentinel Node Biopsy for Oral Cavity Cancer: Establishing the Workflow in Practice

Speakers: David M. Cognetti, MD and Stephen Y. Lai, MD, PhD

Date: Wednesday, September 14

Time: 9:15- 10:15 a.m.

Location: Pennsylvania Convention Center, Room 122AB

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Surgical Consensus Guidelines for SLN Biopsy in Early-Stage Oral Cavity Cancer

Received: 2 March 2019 | Accepted: 5 March 2019
DOI: 10.1002/hed.25739

ORIGINAL ARTICLE

WILEY

Surgical consensus guidelines on sentinel node biopsy (SNB) in patients with oral cancer

Clare Schilling PhD[1] | Sando J. Stoeckli MD[2] | Maurizio G. Vigili MD[3] | Remco de Bree PhD[4] | Stephen Y. Lai MD[5] | Julio Alvarez PhD[6] | Anders Christensen MD[7] | David M. Cognetti MD[8] | Anil K. D'Cruz MD[9] | Bernhard Frerich DMD[10] | Renaud Garrel PhD[11] | Naoyuki Kohno PhD[12] | Willem Martin Klop PhD[13] | Cyrus Kerawala MD[14] | Georges Lawson MD[15] | Jeremy McMahon MD[16] | Isabel Sassoon PhD[17] | Richard J. Shaw MD[18] | Jesper F. Tvedskov PhD[7] | Christian von Buchwald DMSc[7] | Mark McGurk MD[1]

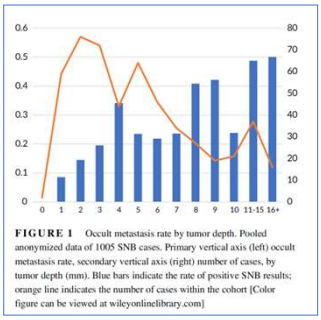

FIGURE 1 Occult metastasis rate by tumor depth. Pooled anonymized data of 1005 SNB cases. Primary vertical axis (left) occult metastasis rate, secondary vertical axis (right) number of cases, by tumor depth (mm). Blue bars indicate the rate of positive SNB results; orange line indicates the number of cases within the cohort [Color figure can be viewed at wileyonlinelibrary.com]

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