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Surgical Management of the N0 Neck in Oral Cavity and Oropharyngeal cancers

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No Conflicts

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Goals

Understand:

- Risks factors that contribute to cervical metastasis in OC/OP SCCA
- Patterns of spread in OC/OP SCCA
- Principles of surgical management and types of neck dissections
- The QOL impact of surgical management of the neck
- Best practices for surgical management of the N0 neck in OC/OP SCCA

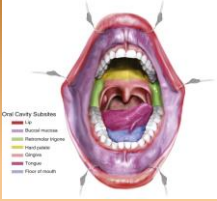
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Background

Fundamental Challenges:


- Occult metastasis- subclinical spread to cervical lymph nodes
- Presence of metastasis reduces survival by ~50%
- Morbidity of neck dissection and avoidance of 'unnecessary' surgery for N0 patients

Oral Cavity



- Upper and lower lips
- Buccal cavity
- Upper and lower alveolus
- Buccal mucosa
- Floor of the mouth
- Anterior 2/3 of tongue
- Hard palate

Oropharynx



- Anterior**
 - base of tongue, vallecula, lingual surface of epiglottis
- Lateral**
 - anterior pillar, palatine tonsil, posterior pillar
- Superior**
 - soft palate (oral side)

Occult Metastasis Rate in END

Study	Rate of Occult Cervical Nodal Metastasis
Mirea et al, 2014 ¹⁸	27.08%
Fakih et al, 1989 ¹⁹	33.33%
Vandenbrouck et al, 1980 ²⁰	49%
Kligerman et al, 1994 ²¹	20.59%
D'Cruz et al, 2015 ²²	29.63%
Yuen et al, 2009 ²³	22%
Mean	30.27%
SD	9.42

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Positive Nodes in OCSCC

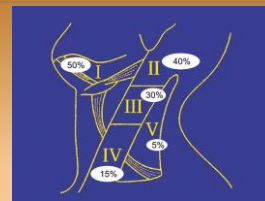
Tumor site	No. (%) of cases	T1 95.7%
Tongue	72 (43)	T2 80.5%
Floor of the mouth	48 (29)	T3 69.1%
Hard palate	6 (4)	T4 60%
Retromolar trigone	17 (10)	N0 89.6%
Cheek	24 (14)	N1 58.8%
Total	167 (100)	N2 57.1%
		N3 56.5%

Tirelli G B/OMS, 2018

Patterns of Spread

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Patterns of Spread



Nodal distribution in HNSCC

- Robert Lindberg: 2044 patients from MD Anderson from years 1948-1965 (Lindberg Cancer, 1972)
- Elegant retrospective study of newly diagnosed SCCHN patients with incidence of primary site and pattern of nodal metastasis. He noted that the frequency and location of nodal metastasis was highly influenced by primary site size and location
- Shah
- 1081 patients from MSK with untreated SCCHN who underwent therapeutic or elective or RND between 1965-1986 (Shah J AJO 1990)
 - 343 Elective ND yielded 33% occult metastasis rate
 - OC: Highest frequency in levels I-III
 - OP: Highest frequency in levels II-IV

Occult Rate for OC and OP SCC

TABLE I
Distribution and Histologic Confirmation of Metastatic Disease by Site in 1,081 Patients Undergoing 1,119 Elective and Therapeutic RNDs

Primary Site	No. of Patients	No. of RNDs	Positive Nodes in Elective RNDs	Positive Nodes in Therapeutic RNDs
Oral cavity	501	516	34% (85/192)	76% (246/324)
Oropharynx	207	213	31% (15/48)	84% (158/165)
Hypopharynx	126	128	17% (4/24)	97% (131/134)
Larynx	247	262	37% (23/79)	84% (155/183)
Total	1,081	1,119	33% (113/343)	82% (640/776)

(Shah J AJO 1990)

Frequency of occult metastasis by level

TABLE II
Percentage of Metastatic Lymph Nodes Involved in Elective and Therapeutic RNDs

Level of Metastatic Lymph Nodes	Primary Site							
	Oral Cavity		Oropharynx		Hypopharynx		Larynx	
	Elective	Therapeutic	Elective	Therapeutic	Elective	Therapeutic	Elective	Therapeutic
I	58	61	7	17	0	10	14	8
II	51	57	80	85	75	78	52	68
III	26	44	60	50	75	75	55	70
IV	9	26	27	33	0	47	24	55
V	2	4	7	11	0	11	7	5

Shah J AJ, 1990

Detection

Table 2 The pooled estimates of different imaging modalities in cNO neck evaluation
From: [Detection of cervical lymph node metastasis in head and neck cancer patients with clinically No neck—a meta-analysis comparing different imaging modalities](#)

Modalities	Sensitivity (95%CI)	Specificity (95%CI)	LR+ (95%CI)	LR- (95%CI)	QUADAS score* (95%CI)
CT	0.52 (0.39~0.65)	0.93 (0.87~0.97)	7.9 (3.6~17.4)	0.51 (0.38~0.68)	8.1 (3.8~12.4)
MRI	0.65 (0.34~0.87)	0.81 (0.64~0.91)	3.4 (1.8~6.2)	0.44 (0.21~0.93)	7.6 (4.1~11.1)
PET	0.66 (0.47~0.80)	0.87 (0.77~0.93)	5.2 (2.6~10.4)	0.39 (0.24~0.65)	10 (6.9~13.1)
US	0.66 (0.54~0.77)	0.78 (0.71~0.83)	3.0 (2.1~4.2)	0.44 (0.3~0.64)	7.5 (3.6~11.4)

* Yes: 1; No/unclear: 0;
± LR: likelihood ratio positive; LR-: likelihood ratio negative.

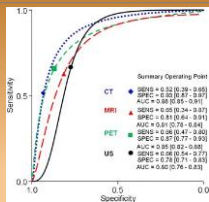
Liao JJ Detection of cervical lymph node metastasis in head and neck cancer patients with clinically NO neck—a meta-analysis comparing different imaging modalities BMC 2012.

Table 3 The positive and negative predictive value of nodal metastasis following imaging exams among various baseline possibilities of neck nodal metastasis
From: [Detection of cervical lymph node metastasis in head and neck cancer patients with clinically No neck—a meta-analysis comparing different imaging modalities](#)

Imaging Modalities	Baseline possibility of neck nodal metastasis	Positive predictive value*	Negative predictive value*
CT	10%	47%	95%
	20%	66%	89%
	30%	77%	82%
MRI	10%	27%	95%
	20%	46%	90%
	30%	59%	84%
PET	10%	36%	96%
	20%	56%	91%
	30%	69%	86%
US	10%	25%	95%
	20%	42%	90%
	30%	56%	84%

* % Possibility of neck nodal metastasis following a "positive" imaging result.
± % Possibility of "silent" neck nodal metastasis following a "negative" imaging result.

Sensitivity Analysis



Neck Dissection

Considerations for surgical treatment of the neck

- Oncologic risk for nodal metastasis
- Location and size of the tumor
- Patient co-morbidities
- Patient and family wishes
- Training of the surgeon

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Pioneers

Crile (1906) *En bloc* lymphadenectomy= Radical Neck Dissection (published 162 procedures)

Martin (1950s)Radical Neck Dissection (published >1400 procedures)

Suarez Functional Neck Dissection (FND)

Bocca Modified Radical Neck Dissection=FND

Byers/Medina Selective neck dissection

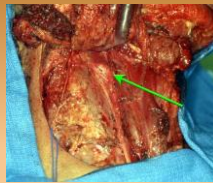
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Radical Neck Dissection



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Modifications



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Types of Neck Dissections

A. Comprehensive

Radical

Modified Radical

type I: (spare XI), II: (spare XI, IJ), III: (spare XI, IJ, SCM)

B. Selective

Lateral

Anteriolateral (supraomohyoid)

Posteriolateral

C. Extended

Complications

- Bleeding
- Infection
- Chylous fistula
- Facial/cerebral edema
- Carotid rupture
- Air embolism
- Shoulder dysfunction

Neck Dissection Quality of Life (QOL)

Shoulder Dysfunction

- Chronic neck and shoulder pain
- Shoulder weakness
- Scapular winging
- Impact on work and leisure
- Cosmetic Defect

Functional Impact

Table 2. Raw data constant's subjective and objective scores by neck dissection type.

Score	SND	MRND	p value
Constant's objective (0-65)	50.8	40.8	.0008
Constant's subjective (0-35)	29.1	22.0	.0017
Constant's total (0-100)	79.9	62.8	.0002

Constant's score = 41.8 - 13.6*ND - 8.7*XRT + 0.60*kg, (R² = 0.44)

Neck Dissection Impairment Index (QOL)

As a result of the cancer **TREATMENT OF YOUR NECK**, how much have you been bothered by the following over the past **4 WEEKS**?

1. Are you bothered by neck or shoulder **pain or discomfort**?
2. Are you bothered by neck or shoulder **stiffness**?
3. Are you bothered by difficulty with **self-care** activities because of your neck or shoulder (for example, combing hair, dressing, bathing, etc)?
4. Have you been limited in your ability to **lift light** objects because of your shoulder or neck?
5. Have you been limited in your ability to **lift heavy** objects because of your shoulder or neck?
6. Have you been limited in your ability to **reach above** for objects because of your shoulder or neck (for example, from shelves, tables, or counters)?
7. Are you bothered by your **overall activity level** because of your shoulder or neck?
8. Has the treatment of your neck affected your participation in **social activities**?
9. Have you been limited in your ability to do **leisure or recreational** activities because of your neck or shoulder?
10. Have you been limited in your ability to do **work** (including **work** at home) because of your neck or shoulder?

NDII = 5.44 + 0.82 (Patient weight) - 13.45 (Radiation Therapy) + 0.30 (Age) - 6.43 (Neck Dissection Type)

NO Neck: To Watch or Treat

Evidence Quality

Level	Type of evidence
I	Large RCTs with clear cut results
II	Small RCTs with unclear results
III	Cohort and case-control studies
IV	Historical cohort or case-control studies
V	Case series, studies with no controls

Grade of Recommendation	Level of Evidence	Type of Study
A	1a	Systematic review of (homogeneous) randomized controlled trials
A	1b	Individual randomized controlled trials (with narrow confidence intervals)
B	2a	Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
B	2b	Individual cohort study / low-quality randomized control studies
B	3a	Systematic review of (homogeneous) case-control studies
B	3b	Individual case-control studies
C	4	Case series, low-quality cohort or case-control studies
D	5	Expert opinions based on non-systematic reviews of results or mechanistic studies

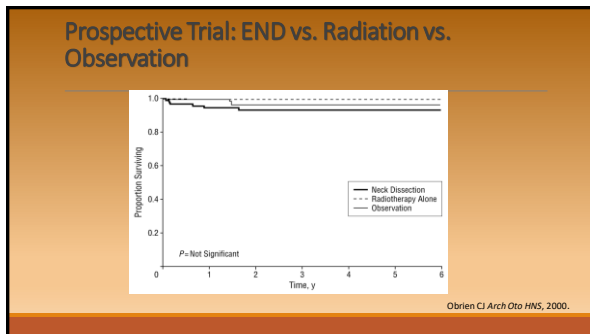
Prospective Trial: END vs. Radiation vs. Observation

T Stage	Neck Dissection	Radiotherapy	Observation	Total
1	11	0	51	62
2	51	5	5	61
3	13	2	1	16
4	21	1	1	23
Total	96	8	58	162

T Stage	No. Dissected	No. (%) Positive
1	11	3 (27)
2	51	18 (35)
3	13	5 (38)
4	21	5 (24)
Oral cavity	75	25 (33)
Oropharynx	21	5 (24)

Level	No. Dissected	No. (%) Positive
I	108	11 (10)
II	108	19 (18)
III	108	9 (8)
IV	52	3 (6)
V	13	0 (0)

Obrien CJ Arch Oto HNS, 2000.



Summary of Randomized Trials

Study	Elective therapy	Total patients	Occult metastasis on END ^a	Regional involvement on observation	Salvage ^b	Rate of DFS ^c
Vandenbrouck et al [21]	RND	75	49% (9%)	47%	Not reported	46% (58%) at 3 years
Fakih et al [55]	RND	70	33% (14%)	57%	22% (30%)	64% (53%) at 12 months
Klugerman et al [54]	SND	67	33% (12%)	39%	25% (27%)	72% (49%) at 3 years

^a Numbers in parentheses indicates neck recurrences after END.
^b Salvage rates in neck recurrences only. Numbers in parentheses indicate salvage rates for neck recurrences in observation group. Minimum follow-up time shown.
^c Numbers in parentheses indicate DFS in observation group.
^d Study is specific to oral tongue SCC.

Summary of Randomized Trials

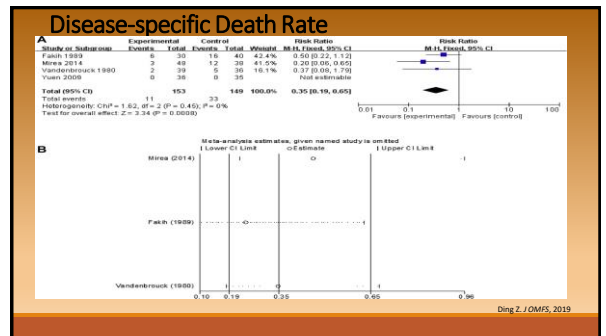
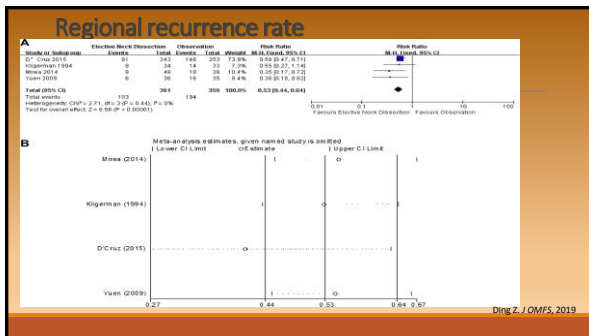
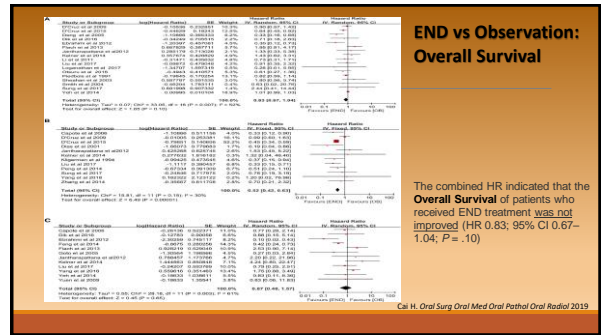
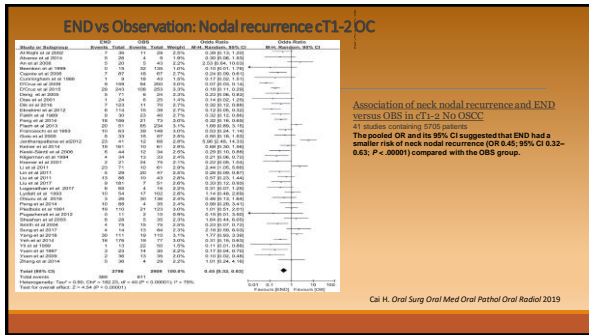
Study	Elective therapy	Total patients	Occult metastasis on END ^a	Regional involvement on observation	Salvage ^b	Rate of DFS ^c
Khafif et al [65]	RND	590	42% (13%)	19%	49%	68% (88%) at 3 years
Nieuwenhuis et al [63]	N/A	161	N/A	21%	(79%)	(79%) at 12 months
Duwart et al [59]	SND	359	23% (8%)	27%	Not reported	66% (54%) at 3 years
Keski-Santti et al [60]	SND, RT or SND+RT	80	34% (13%)	24%	11% (47%) ^d	82% (81%) at 3 years
Capote et al [31]	END	154	Not reported (8%)	26.8%	32% ^d	92.5% (71.2%) at 5 years

^a Numbers in parentheses indicates neck recurrences after END.
^b Salvage rates in neck recurrences only. Numbers in parentheses indicate salvage rates for neck recurrences in observation group. Minimum follow-up time shown.
^c Numbers in parentheses indicate DFS in observation group.
^d Study is specific to oral tongue SCC.

Meta-analysis of Prospective trials END for NO neck

Study	Design	Year of Accrual	Sample Size, N	Age (yr)	Male/Female	Site
Mirea et al, ¹⁰ 2014 (Romania)	Prospective randomized matched case-and-control study	2000.1-2005.1	86	Mean 54	69/17	AT
Fakih et al, ¹⁹ 1989 (India)	Prospective randomized trial	1985.7-1988.9	70	NA	45/25	AT
Vandenbrouck et al, ²⁰ 1980 (France)	Randomized trial	1966.12-1973.7	75	Mean 57	67/8	AT, FM
Klugerman et al, ²¹ 1994 (Brazil)	Prospective randomized study	1987-1992	67	Median 57	52/15	AT, FM
D'Cruz et al, ²² 2015 (India)	Prospective randomized, controlled trial	2004.1-2014.6	496	Mean 48	374/122	AT, BM, FM
Yuen et al, ²³ 2009 (Hong Kong)	Prospective randomized study	1996-2004	71	Mean 57	43/28	AT

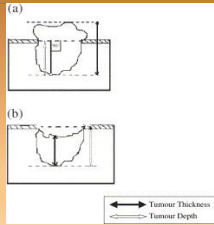
Ding Z. J OMSF, 2019



Risk factors for regional metastasis

- ### Risk Factors for occult disease
- Tumor size
 - Perineural invasion
 - Lympho-vascular invasion
 - Depth of invasion
 - Close/positive margins
 - Tumor microenvironment

Prognostic impact of cervical metastasis



Kane SV. ESO, 32 (7): 2006

DOI introduced into staging for OCSCC

T category	Maximum diameter	Depth of invasion
T1	≤ 2 cm	≤ 5 mm
T2	≤ 2 cm	5–10 mm
or	2–4 cm	≤ 10 mm
T3	> 4 cm	
or		> 10 mm
T4	Advanced disease invading bone or adjacent structures	

Molecular Predictors of nodal metastasis

Molecular marker	Role in carcinogenesis/metastasis	Method of molecular evaluation
TP53	Most commonly mutated locus in human cancers TP53 arrests cell cycle to DNA repair; damaged cells can be removed by inducing apoptosis [111120]	Direct sequencing of exons 4-9 from genomic DNA [151154]
Cyclin D1	Overexpression in 68% of oral SCCs [100] Overexpression correlates with lymph node metastasis and poor outcome [10114]	Immunohistochemistry [100]
EGFR	Levels correlate with lymph node metastasis and poor outcome [116117]	Immunohistochemistry [116]
E-cadherin	Lower levels are associated with a metastatic phenotype in head and neck SCCs [115116] and tumor specimens [18]	Immunohistochemistry [119]
MMP-9	Increased levels have been associated with invasiveness of oral SCC and metastasis [151156]	Immunohistochemistry [157]
uPA	uPA expression correlates with invasion and metastasis [158] Blockage of uPA abrogates SCC invasion [159]	Immunohistochemistry [158]
VEGF	Binding of VEGF induces proangiogenesis and/or glymphangiogenesis pathways. Overexpression correlated to lymphatic spread in some tumors. Not an independent predictor of neck metastasis in oral cavity SCC [109]	Immunohistochemistry [100]

Cheng A. OMSF Clin N Amer, 2008.

Factors associated with occult neck metastasis (Mair 2018)

Factors	Univariate analysis P – value	Multivariate analysis Two sided P-value (Odds ratio)	95% confidence interval
Age	0.076	–	–
T stage	0.235	–	–
T dimension	0.67	–	–
LVE	1.000	–	–
PNI	0.006	0.447 (0.790)	0.430–1.452
Site of tumor (Tongue vs Buccal mucosa)	0.001	0.089 (0.642)	0.385–1.070
Grade	0.001	0.082 (0.573)	0.306–1.074
Margins	0.113	–	–
Thickness ≤ 5 mm	0.000	0.000 (3.255)	1.733–5.985
Type of tumor	0.004	0.087 (0.639)	0.382–1.068

354 patients with 28.5% occult metastasis rate and 15.3% ECS. ECS was 48% and 29% in lymph nodes smaller than 10mm and 5mm respectively.

Chi-square test.
** Logistic regression.

Mair M. Oral Oncology, 2018.

Prospective Randomized Control Trial

- 596 patient prospectively randomized for elective neck dissection (END) versus watchful waiting and therapeutic neck dissection
- T1 or T2 OCSCC (lateralized)
- Neck dissection= ipsilateral SND
- Adjuvant RT: node+, DOI>10mm, margin+, +/- PNI or LVI
- Mean follow up: 39 months
- Outcomes: OS and DFS

D'Cruz NEJM, 2015.

Patient Characteristics

Table 3. Characteristics of the Patients at Baseline.*

Characteristic	Elective-Surgery Group (N = 243)	Therapeutic-Surgery Group (N = 253)	All Patients (N = 496)
Mean age (range) — yr	48 (21–75)	48 (20–75)	48 (20–75)
Sex			
Male	187 (77.0)	187 (73.9)	374 (75.4)
Female	56 (23.0)	66 (26.1)	122 (24.6)
Site of primary tumor			
Tongue	207 (85.2)	216 (85.4)	423 (85.3)
Buccal mucosa	33 (13.6)	33 (13.0)	66 (13.7)
Floor of mouth	3 (1.2)	2 (0.8)	5 (1.0)
Tumor stage			
T1	105 (43.2)	114 (45.1)	219 (44.2)
T2	138 (56.8)	139 (54.9)	277 (55.8)
Baseline ultrasonography			
Normal	222 (91.4)	234 (92.5)	456 (91.9)
Indeterminate	19 (7.8)	17 (6.7)	36 (7.3)
Suspicious	2 (0.8)	2 (0.8)	4 (0.8)

* There were no significant differences between the two groups. Additional information regarding baseline characteristics is provided in Table S1 in the Supplementary Appendix.

D'Cruz NEJM, 2015.

