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### Surgical Management of the NO Neck in Oral Cavity and Oropharyngeal cancers

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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  $\ensuremath{\mathsf{SCCA}}$

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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

Anterio

### **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



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









## Impact of cervical metastasis

N category		Size of metastasis	ENE	
NO	No nodal metastasis			
N1	Metastasis in a single ipsilateral node.	s3 cm	No	
		42		
N2a	Metastasis in a single ipsilateral node	3-6 cm	No	
N2b	Metastasis in multiple ipsilateral nodes	s6 cm	No	
N2c	Metastasis in bilateral or contralateral nodes	s6 cm	No	
		43		
N3a	Metastasis in any lymph node	>6 cm	No	
N3b	Metastasis in any lymph node	Any	Yes	
	*ENE: extran	odal extension		

### **Occult Metastasis Rate in END**

Table 5Rates of Occult Cervical Lymph Node Metastasis in Inc	luded Studies
	Rate of Occult Cervical Nodal Metastasis
Mirea et al, 2014 <sup>18</sup>	27.08%
Fakih et al, 1989 <sup>19</sup>	33.33%
Vandenbrouck et al, 1980 <sup>20</sup>	49%
Kligerman et al, 1994 <sup>21</sup>	20.59%
D'Cruz et al, 2015 <sup>22</sup>	29.63%
Yuen et al, 2009 <sup>23</sup>	22%
Mean	30.27%
SD	9.42

Posi	tive	Nodes in OCSCC
1 00.		
Tumor site	No. (%) of cases	T1 95.7% T2 80.5%
Tongue	72 (43)	T3 69.1%
Floor of the mouth	48 (29)	T4 60%
Hard palate	6 (4)	N0 89.6%
Retromolar trigone	17 (10)	N158.8% N2 57.1% N3 55.5%
Cheek	24 (14)	
	167 (100)	

### Patterns of Spread

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### **Nodal distribution in HNSCC**

Robert Lindberg: 2044 patients from MD Anderson from years 1948-1965 (Undbeg Cancer, 1972) "Elegant retrospective study of newly diagnosed SCCNN 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 the rapeutic or elective or RND between 1965-1986 (shah ) AUS 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

		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% (65/192)	76% (246/324)
Oropharynx	207	213	31% (15/48)	84% (138/165)
Hypopharyttx	126	128	17% (4/24)	97% (101/104)
Larvitx	247	262	37% (29/79)	84% (155/183)
Total	1.081	1.119	33% (113/343)	82% (640/776)

TABLE II	II Percentage of Metastatic Lymph Nodes Involved in Elective and Therapeutic RNDs							
Level of	Primary Site							
Metastatic Lymph Nodes	Elective	Therapeutic	Elective	Therapeutic	Elective	Therapeutic	Elective	Therapeutic
	5.8	61	7	17	0	10	14	8
	51	57	80	85	75	78	52	68
12010	26	44	60	50	75	75	55	70
	0	20	27	33	0	47	24	35
	2	4	7	11	0	11	7	5



Modalities	Sensitivity (95%CI)	Specificity (95%CI)	LR + (95%CI)	LR- (95%CI)	QUADAS score' (95%CI)
ст	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)

Table 3 The positive and negative predictive value of nodal metastasis following imaging exams among various baseline possibilities of neck
nodal metastasis
New 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
ст	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%



### **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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### **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

### . 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**

score	SND	MRND	<i>p</i> 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

### 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?

- Leen domented by me tomoving over the pairs **a vector** Are you bothered by neck or shoulder **pain or disconfort?** Are you bothered by difficulty with **self-care** activities because of your neck or shoulder **difficulty**.
- Have you been limited in your ability to lift light objects because of your shoulder or neck?
- Have you been limited in your ability to lift heavy objects because of your shoulder or neck?
- 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)? Are you bothered by your overall activity level because of your shoulder or neck?
- or neck? 8. Has the treatment of you 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?
- because of your neck or shoulder? 10. Have you been limited in your ability to do werk (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

Level	Type of evidence
ı .	Large RCTs with clear cut results
	Small RCTs with unclear results
	Cohort and case-control studies
IV .	Historical cohort or case-control studies
v	Case series, studies with no controls

Grade Recomme	e of ndation	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)
в	2a		Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
В	2b		Individual cohort study / low-quality randomized control studies
в	3a		Systematic review of (homogeneous) case-control studies
в	3b		Individual case-control studies
с	4		Case series, low-quality cohort or case- control studies
D	5		Expert opinions based on non-systematic reviews of results or mechanistic studies

	005	CI Va	uon							
Table 3. Nexk Treatment Based on Tumor Stage				Table 6. Correlati With T Stage and	on of Pathological N Site	iode Status	Table 5. Pathological Nadal Distribution for 108 Neck Dissections			
⊺ Stage	Neck Dissection	Radiotherapy	Observation	Total	T Stage	No. Dissected	No. (%) Positive	Level	No. Dissected	No. (%) Posit
1	11	0	51	62	1	11	3 (27)		108	11/17/
2	51	5	5	61	2	51	18 (35)	1	100	19/18
3	13	2	1	16	3	13	5 (38)	i i	108	9.(8)
4	21	1	1	23	Oral cavity	75	25 (33)	N	52	3 (6)
Total	96	8	58	162	Oropharynx	21	5 (24)	V	13	0(0)



Study	Elective therapy	Total patients	Occult metastasis on END <sup>a</sup>	Regional involvement on observation	Salvage	Rate of DFS <sup>®</sup>
/andenbrouck 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
Kligerman et	SND	67	33% (12%)	39%	25% (27%)	72% (49%) at 3 years

Study	Elective therapy	Total patients	Occult metastasis on END	Regional involvement on observation	Salvage"	Rate of DFS
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
Duvvuri 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%) *	82% (81%) at 3 years
Capote et al [31]	END	154	Not reported (8%)	26.8%	32%	92.5% (71.2%) at 5 years

Table 1Characteristi	s of Included Studies	(Part 1)				
Study	Design	Year of Accrual	Sample Size, N	Age (yr)	Male/Female	Site
Mirea et al, <sup>18</sup> 2014 (Romania)	Prospective randomized matched case-and- control study	2000.1-2005.1	86	Mean 54	69/17	AT
Fakih et al, <sup>19</sup> 1989 (India)	Prospective randomized trial	1985.7-1988.9	70	NA	45/25	AT
Vandenbrouck et al, <sup>20</sup> 1980 (France)	Randomized trial	1966.12-1973.7	75	Mean 57	67/8	AT, FM
Kligerman et al, <sup>21</sup> 1994 (Brazil)	Prospective randomized study	1987-1992	67	Median 57	52/15	AT, FM
D'Cruz et al, <sup>22</sup> 2015 (India)	Prospective randomized, controlled trial	2004.1-2014.6	496	Mean 48	374/122	AT, BM, FM
Yuen et al, <sup>23</sup> 2009 (Hong Kong)	Prospective randomized study	1996-2004	71	Mean 57	43/28	AT

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to make at us prove		- 24	11	278	2.015	0.000.00.10.10.1000			
Advanted at us 2004		24	4		1.0%	0.30 (0.06, 1.83)			
5e-et al 2008	5	- 20	5	-40	8.2%	2.55 81.64, 10.008			
Beendeen of all 1998		2.83	32	1288	1.0%	0.10 35 01, 1.74	• • •	-	
Depote et al 2008	1.7	87	- 15	- 67	2,7%	0.248.00, 0.612			
Durwinghaies ar ar 1966	1.1	. 9	10	43	1.0%	0.17 81.00, 1.61			
Printer of all 2008		1.93		200	3.0%	0.07 pi.co. 0.541			
PCFUE of all 2015	29	243	100	250	0.0%	0.103011,0.26			
and a way of the	- 22	- 65	e.	- 25	4.3%	0.00 (0.06) 0.82[			
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30: 01 21 22:10		122.4	22	10		0.32 81.12, 0.881	in the second se		Association of neck notal recurrence and END
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frame of at 19714		100	- 51	- 22	3.000	0.10.10.10.0.001			versus Obs III c11-2 NO OSCC
Teeth at al 2013	20	- 10		234	3.1%	1,601 20,600, 3,152			41 studies containing 5705 patients
Interconcept and an entrants	10		100	140	3.0%	0.52 8 24 1 141			+1 studies containing 5705 patients
Table at at 2000	1.00		10	87	2.0%	0.00 10.10, 1.800			The pooled OR and its 95% CI suggested that END had a
orthanapatane or al2012	22	.41	12	60	2.0%	5.001240.14.331			and the state of a set of a set of a set of a set of the other of the set
Celline' el al 2014	10	191	10	81	2.8%	Q AM RD 200, 1 (Hell			smaller risk of neck hodal recurrence (OK 0.45, 55% CI 0.52=
Genit-Silent at al 2000	. 6	.44	12	- 74	2.9%	0.293510,0.882			0.63: P < 00001) compared with the OBS group
tilgermen et al 1994		- 24	12	- 22	2.4%	0.21 81.06. 0.725			
Converse ad ad 2001		23	24	78	2.5%	0.257 25.06. 1.042			
J att of 2011	20	7.5	10	01	2.9%	2.4411.05.5.661			
an ed. of 20111		22.0	20	. 67	3.8%	Q 280 82 000, 03.871			
As at of 2011	53	- 65	10	- 43	2.0%	0.57 (0.25, 1.44)			
Ju 48.04 2017		185	- 2	51	2.0%	0.2230.12, 0.931			
regeneratives at al. 2017		- 05	4	10	2.2%	0.31 91.07, 1.280			
What of of 1993	40	- 04		102	2.0%	1.14 33.40, 2.000			
Charles on one will be		- 24	30	1.000	4.4%	to me pl 13, 1,64			
The second second	20	- 00		- 00	2.475	0.00 8120, 3.411			
manues to se 1991	19	- 50	- K.	- 23	0.17%	1.01 (0.51, 2.01)			
Rendered at al Didd's		100	- 12 I	- 25	0.0014	3 00 10 44 0 001			
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ranget at 2018	20	111	19	110	3.1%	1,77 81,99, 0,981			
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73 at at 1990	1	10	22	- 60	1.0%	0.11 81.01, 0.881			
Factor at all 1997		123	14	349	2.2%	0.17 81.04, 0.781			
familied at 2009	2	- 36	13	395	2.0%	0.1035.02, 0.481			
2nang-ot at 2014	- 6	:00		29	2.2%	1.01 (0.24, 4.16)			
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tung avecas	380	-	411						
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	1.0x #4.00 2017 F	-0.0007.8	0.4798344	4.3%	10.023 80.000. 21.0023		
	Loperation et al 2017	-1.34707	1.807310	4.44	6.24 (0.01, 6.03)		
	Observation 2016	-0.8953	0.410571	5.3%	0.44 (0.47, 1.46)		
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	5. ha left ad 200 K F	-0.24207	0.00112010	10.0%	0.75 (0.25. 2.01)	-	
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## 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



### 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	
тз	> 4 cm		
or		> 10 mm	
Τ4	Advanced disease invading bone or adjacent structures		

Molecular marker	Role in carcinogenesis/metastasis	Method of molecular evaluation		
TP53	Most commonly mutated locus in human cancers	Direct sequencing of exons 4–9 from genomic DNA [153154]		
	7P53 arrests cell cycle so DNA repair can occur or damaged cells can be removed by inducing apoptosis [111120]			
Cyclin D1	Overexpressed in 68% of oral SCCs [110]	Immunohistochemistry [110]		
	Overexpression correlates with lymph node metastasis and poor outcome [110114]			
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 SCC lines [115119] and tumor specimens [118]	Immunohistochemistry [119]		
MMP-9	Increased levels have been associated with invasiveness of oral SCC and metastasis [155156]	Immunohistochemistry [157]		
uPA	uPA expression correlates with invasion and metastasis [158]	Immunohistochemistry [158]		
	Blockage of uPA abrogates SCC invasion [159]			
VEGFR	Binding of VEGF induces proangiogenesis and/or prolymphangiogenesis pathways	Immunohistochemistry [103]		
	Overexpression correlated to lymphatic spread in some tumors			
	Not an independent predictor of neck metastasis in oral cavity SCC [103]			

Factors	Univariate analysis two sided P – value	Multivariate analysis Ttwo sided P- value (Odds ratio)	95% confidence interval	
Age	0.076	-	-	
T stage	0.235	-	-	354 patients with 28.5%
T dimension	0.67	-	-	and 15 3% FCS_FCS was
LVE	1.000	-	-	48% and 29% in lymph
PNI	0.006	0.447 (0.790)	0.430-1.452	nodes smaller than
Site of tumor (Tongue vsBuccal mucosa)	0.001	0.089 (0.642)	0.385-1.070	10mm and 5mm respectively.
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	

Factors associated with occult neck metastasis (Mair 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)

D'Cruz NEJM, 2015.

•Neck dissection= ipsilateral SND

•Adjuvant RT: node+, DOI>10mm,margin+, +/- PNI or LVI

•Mean follow up: 39 months

•Outcomes: OS and DFS

### Patient Characteristics

Characteristic	Elective-Surgery Group (N = 243)	Therapeutic-Surgery Group (N = 253)	All Patients (N = 496)
		number (percent)	
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)	35 (13.8)	68 (13.7)
Floor of mouth	3 (1.2)	2 (0.8)	5 (1.0)
Turnor stage			
та	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)

	10	-					Subgroup	flective Surgery	Therapeutie Surgery	Hazard Ratio (85% CI)	P Value fa Interaction
	0.8	-			Dective as	ingery	Common the				11.10
3			-	-		a break	Barrel Property	8/33	8.02		
72	0.6-			T	empountic out	TILL I'V	Torona or Borr of rooms	41/110	PE-018	-	
8	331						Sep.			_	0.34
1	0.4-						n	21/025	28124		
	Plax	and ratio, 0.4	H (05% CL 0	45-0.92)			- 12	25/334	\$1/129		
	0.3-						See .				0.65
2							Remain	00/55	18.098		
	0.0		1		1.		Mala	40,047	\$1,187		
	0	- 12	24	30	44	60	Unoccapate				0.74
			onths since t	Randomizat	ion .		Indident transmist ar subplained	7/21	8/12	international data in the local data in the loca	
n. at Hisk			12.22		1.11		ficental	45/222	73(234		
scarpendic	243	192	1.42	105	10	24	UK or PMI				0.34
surgery							Abrel	18(20)	18/128		
							Roset	9/25	35/97		
Disease-free	Survival						inimitagie grade				0.54
-	10	201					Popely all fermitated	00/99	2014		
1	1	-					Walter motionary differentiated	36(387	13/195	-8-	
	0.8-	-	· · · · · ·				Reactor mage				0.5#
	22	1			Elerchive be	angoiry.	Negative	m(231	78/042		
-	0.6-					and the second	Restor	3/8	1,5		· · · · · · · · · · · · · · · · · · ·
			states - same in some				Redictorary				0.82
4	0.4-			77	erapeutit ber	THEFT.	Ret	13/504	141488		
4	Haz	ard natio, 0.4	13 (93% Cl. O.	34-0.59)			10	37(119	80(11)		
3	0.3- P<0	001					Tumor depth				0.12
2							-siren	8(34	413		
	0.0.1	15	24	16	44	20	13.4641	41/178	14/235	-	
			oothe since it	Pandomirat			Alipsiers	50/243	78(055		
										-	
o. at Risk	243	170	126	-	21	52				0.2	

Results

•END: 81 recurrences •Deaths: 79 deaths •DFS: 69.5% •OS: 80.1% •HR: 0.64 (p=0.01) •WW: 146 recurrences •Deaths: 79 deaths •DFS: 45.9% •OS: 67.5%

### Summary

- •Surgical management of the neck has evolved, balancing oncologic risks, morbidity and patient factors
- •Pathologic features of the primary tumor impact the likelihood of occult disease: tumor size, depth of invasion, perineural invasion
- •Elective management of the NO neck confers overall and disease free survival when high risk features are present