

DEBATE: Should Surgery Be Considered the Standard of Care in Low-Risk HPV-Related OPC?

NO

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• Retrospective Comparisons:



DeVirgilio *Eur Arch ORL* 2020 Bollig *H*&*N* 2022



BIAS

a.k.a. confounding



• Retrospective Comparisons:



aHR 1.9 95%CI 1.3-2.7 p<0.001

adjusted for age, comorbidity, stage, subsite

DeVirgilio Eur Arch ORL 2020 Bollig H&N 2022



Importance of Surgical Candidacy

- retrospective series of 143 patients all treated with (chemo)radiotherapy
- categorized as TORS-favorable versus TORS-unfavorable based on clinical exam and imaging



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MVA	aHR (95%Cl)									
OS	0.12 (0.02-0.62)									
DFS	0.15 (0.03-0.69)									
RFS	0.27 (0.09-0.79)									

adjusted for age, sex, tobacco, alcohol, T, N

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VS







RANDOMIZATION



Hierarchy of Evidence



Why Surgery Should <u>NOT</u> be the Standard of Care in Low-Risk HPVOPC

1) comparable oncologic endpoints

2) no advantage in toxicity or QoL with surgery

3) certainty preferred to rolling the dice

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1) Comparable Oncologic Endpoints

• ORATOR

- phase II, <u>randomized</u>, multi-site trial
- enrolled 68 patients with OPSCC (p16+/-), cT1-2 N0-2 (AJCC7)



1) Comparable Oncologic Endpoints

• ORATOR

• all patients (88% p16+)



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MDADI Demonstrates Insult in Swallowing QoL After TORS

- <u>MD</u> <u>A</u>nderson <u>D</u>ysphagia <u>I</u>ndex
 - 4 subscales: global, emotional, functional, physical
 - 2 composite scales: total, composite
 - all scored 20-100, with higher scores indicating better QoL
 - clinically meaningful difference: ≥ 10 points

• Primary Endpoint of ORATOR: MDADI Total Score at 1 year

MDADI Demonstrates Insult in Swallowing QoL After TORS

• <u>MD</u> <u>A</u>nderson <u>D</u>ysphagia <u>I</u>ndex

	1 year				Clinically mea			
	RT group	TORS + ND group	Effect estimate (95% CI)	p value†	RT group	TORS + ND group	p value	
Total (primary endpoint)	86.9 (11.4)	80.1 (13.0)	6·7 (0·2 to 13·2)	0.042	7/27 (26%)	11/27 (41%)	0.25	DT hattan
Global	89.6 (15.1)	79·3 (22·6)	10·3 (0·2 to 20·4)	0.046	6/27 (22%)	14/27 (52%)	0.024	RI better
Emotional	88.8 (12.0)	81·3 (12·5)	7·4 (0·9 to 14·0)	0.027	5/27 (19%)	13/27 (48%)	0.021	
Functional	89.9 (11.5)	86.5 (12.0)	3·4 (-2·9 to 9·6)	0.28	7/27 (26%)	9/26 (35%)	0.49	
Physical	83.1 (14.1)	75-3 (16-5)	7·9 (-0·3 to 16·0)	0.058	12/27 (44%)	16/27 (59%)	0.28	TORS better
Composite (total score excluding global score)	86·7 <mark>(</mark> 11·4)	80-2 (13-1)	6·5 (0·0 to 13·1)	0.049	6/27 <mark>(</mark> 22%)	11/27 (41%)	0.14	

Data are presented as mean (SD) unless otherwise stated. RT=radiotherapy. TORS + ND=transoral robotic surgery and neck dissection. *Defined as a decrease of at least 10 points. †p values adjusted for stratification by p16 status (post-hoc analysis): total (p=0.054), global (p=0.071), emotional (p=0.040), functional (p=0.29), physical (p=0.064), and composite (p=0.062).

Table 2: Quality-of-life scores at 1 year for the MD Anderson Dysphagia Inventory

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MDADI Demonstrates Insult in Swallowing QoL After TORS <u>MD Anderson Dysphagia Index</u>

	Basel	ine, Mean ± SD	Yeai Yeai	Year 2, Mean \pm SD Year 3, Mean \pm SD			Difference From Baseline at Year 2, Mean ± SD Year 3, Mean ± SD			Percentage of Patients With CMC ^a at Year 2, % Year 3, %			
Variable	RT Arm (n = 32)	TORS + ND Arm $(n = 32)$	Р	RT Arm (Y2: n = 24) (Y3: n = 25)	TORS + ND Arm (Y2: n = 29) (Y3: n = 26)	Р	RT Arm (Y2: n = 24) (Y3: n = 25)	TORS + ND Arm (Y2: n = 29) (Y3: n = 26)	Р	RT Arm	TORS + ND Arm	Р	LMM, <i>P</i>
Global	91.3 ± 20.3	90.6 ± 18.3	.90	87.5 ± 20.3 93.6 ± 13.8	92.4 ± 13.5 86.9 ± 21.9	.32 .20	-3.3 ± 27.5 1.6 ± 24.4	0.0 ± 20.0 -4.8 ± 27.3	.63 .39	25.0 20.0	18.5 24.0	.57 .73	.18
Emotional	91.1 ± 13.4	87.8 ± 12.0	.30	86.0 ± 13.9 88.8 ± 10.5	83.4 ± 13.3 81.5 ± 13.7	.50 .039	-3.5 ± 18.9 -1.2 ± 17.6	-5.8 ± 14.1 -6.8 ± 12.1	.62 .20	37.5 32.0	37.0 40.0	.97 .56	< .001
Functional	91.6 ± 14.3	90.5 ± 10.6	.71	90.2 ± 12.0 91.7 ± 11.0	89.2 ± 11.4 87.7 ± 14.0	.78 .26	-0.8 ± 16.3 -0.3 ± 17.5	-1.3 ± 12.4 -3.0 ± 14.3	.90 .56	25.0 28.0	29.6 25.0	.71 .81	.066
Physical	91.4 ± 17.5	87.7 ± 15.9	.38	83.3 ± 15.9 86.6 ± 16.6	82.2 ± 15.9 81.4 ± 16.8	.79 .27	-7.3 ± 22.4 -5.2 ± 25.2	-7.1 ± 17.9 -6.8 ± 14.4	.98 .79	41.7 36.0	40.7 36.0	.95 > .99	.020
Total	91.4 ± 14.7	88.3 ± 12.7	.38	86.0 ± 13.5 88.9 ± 11.3	84.8 ± 12.5 83.3 ± 13.9	.74 .12	-4.3 ± 18.9 -2.4 ± 19.3	-4.9 ± 13.4 -5.8 ± 11.7	.90 .47	33.3 32.0	33.3 32.0	> .99 > .99	.049
Composite (excl. global)	91.4 ± 14.5	88.2 ± 12.8	.36	86.0 ± 13.4 88.6 ± 11.3	84.4 ± 12.6 83.1 ± 13.7	.67 .12	-4.4 ± 18.6 -2.7 ± 19.1	-5.2 ± 13.7 -5.8 ± 11.6	.86 .48	33.3 28.0	33.3 32.0	> .99 .76	.033

 TABLE 2.
 Quality-of-Life Scores at 2 and 3 Years for the MD Anderson Dysphagia Inventory

NOTE. Defined as decrease of at least 10 points.

Abbreviations: CMC, clinically meaningful change; LMM, linear mixed modeling; RT, radiotherapy; SD, standard deviation; TORS + ND, transoral robotic surgery plus neck dissection; Y, year. ^aP values < .05 shown as bold.

RT better

TORS better

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MDADI Demonstrates Insult in Swallowing QoL After TORS maybe influenced by primary site?

Variable	Baseline – mean ± SD			Year 2 – mean ± SD Year 3 – mean ± SD			Difference from Baseline at: Year 2 – mean ± SD Year 3 – mean ± SD			F patie	Percentage of patients with CMC ¹ at: Year 2 – % Year 3 – %			
	RT Arm	TORS +ND Arm	P- value	RT Arm	TORS +ND Arm	P- value	RT Arm	TORS +ND Arm	P- value	RT Arm	TORS+ ND Arm	P- value	values	RT better
Tonsil (n=5	0)													
Total	90.7 ± 16.4	90.6 ± 11.4	0.978	84.5 ± 13.1 87.0 ± 11.8	84.9 ± 11.1 83.5 ± 12.8	0.924 0.398	-5.6 ± 20.8 -3.4 ± 21.3	-6.4 ± 11.9 -8.3 ± 10.1	0.885 0.368	36.8 40.0	27.8 37.5	0.556 0.879	0.644	
Composite (excl.	90.7 ± 16.2	90.5 ± 11.6	0.949	84.5 ± 12.9 86.7 ± 11.8	84.5 ± 11.3 83.2 ± 12.6	> 0.99 0.397	-5.6 ± 20.4 -3.6 ± 21.2	-6.7 ± 12.2 -8.4 ± 9.7	0.839 0.373	36.8 35.0	27.8 37.5	0.556 0.877	0.525	TORS better
Base of To	ngue (n=	18)						•	•	•		•	•	
Total	93.4 ± 8.1	83.3 ± 14.6	0.085	91.8 ± 14.7 96.6 ± 3.8	84.7 ± 16.0 82.8 ± 16.6	0.422 0.040	0.4 ± 9.1 1.2 ± 6.2	-2.0 ± 16.4 -1.3 ± 13.6	0.731 0.649	20.0 0.0	44.4 22.2	0.580 0.506	< 0.001	
Composite (excl. Global)	93.3 ± 8.2	83.2 ± 14.5	0.081	91.6 ± 15.1 96.4 ± 4.0	84.3 ± 15.8 82.7 ± 16.5	0.420 0.040	0.2 ± 9.3 1.1 ± 6.2	-2.1 ± 16.6 -1.2 ± 13.7	0.744 0.676	20.0 0.0	44.4 22.2	0.580 0.506	< 0.001	

RT – Radiotherapy; TORS+ND – Transoral robotic surgery plus neck dissection; LMM – Linear mixed modelling; P-values < 0.05 shown as BOLD; ¹Defined as decrease of at least 10 points compared to baseline.

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MDADI Demonstrates Insult in Swallowing QoL After TORS

• <u>MD</u> <u>Anderson</u> <u>Dysphagia</u> <u>Index</u>



MDADI Demonstrates Insult in Swallowing QoL After TORS irrespective of adjuvant therapy

	TORS+ND	TORS+ND + aRT	TORS+ND + aCRT	p	(C)RT
MDADI total (1yr)	82.8	78.5	80.4	0.76	86.9
MDADI total (2yr)	86.1	85.6	81.7	0.76	86.0
	83.7	83.5	81.9	0.97	88.9

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Adding (C)RT to TORS does not significantly affect toxicity.

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Adding (C)RT to TORS does not significantly affect toxicity. **RT is not the problem!**

2)

It's me, Hi. I'm the problem, it's me.

S

Other QoL Instruments Demonstrate No Metric with Significant Advantage with TORS EORTC QLQC30 EORTC H&N35 NDII PNQ FOIS VHI-10

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Toxicity Events with Significant Differences

,	RT Arm					TORS + ND Arm					
AE	G1	G2	G3	G4	G5	G1	G2	G3	G4	G5	Ρ
Constipation	5	4	—	—	—	2	—	—	—	_	.037
Cough	3	_	_	_	—	9	2	—	_	—	.040
Hearing loss (on the basis of audiogram)	5	2	6	—	—	5	_	_	—	—	.028
Neutropenia	—	3	2	1	_	—	—	—	_	_	.025
Other pain	5	7	1	—	—	8	15	1		—	.038
Tinnitus	11	_	1	_	_	2	—	—	—	-	.0055
Trismus	1	—	—	—	—	6	2	1	—	—	.020
Weakness (subjective)	2	2	_	_	_	10	1	_			.030

TABLE 3. Summary of AEs Significantly Different Between Treatment Arms

NOTE. Complete list of AEs is reported in the Data Supplement.

Abbreviations: AE, adverse event; G, grade; RT, radiotherapy; TORS + ND, transoral robotic surgery plus neck dissection.



TORS better

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ORATOR (TORS+ND arm)

• 34 patients



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How should we treat HPV-related OPSCC?