

Characterizing Adverse Determinants of Survival in HPV-Positive Oropharyngeal Cancer Patients Undergoing Unimodality Therapy: A National Cancer Database Retrospective Cohort Analysis

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Abstract

Introduction: Over 10% of patients with human papillomavirus (HPV)-positive oropharyngeal cancer (OPC) undergo surgery alone or radiation alone, yet precise eligibility criteria for unimodal treatment are not well characterized.

Methods: Retrospective cohort study of newly diagnosed HPV+ OPC patients from 2010-2016 using the National Cancer Database who were treated with either primary surgery alone (including neck dissection with ≥ 12 nodes) or definitive radiation therapy (66-72 Gy) alone. Cox proportional hazard analyses were performed to evaluate associations between treatment paradigm, along with other exposures, and overall mortality. Definitions: modified AJCC8 clinical stage IA: cTx/T0/T1; AJCC7 cN0/N1/N2a; IB: cTx/T0/T1, AJCC7 cN2b OR cT2, AJCC7 cN0/N1/N2a/N2b.

Results: Among 1076 identified HPV+ OPC patients, 697 were treated with surgery alone and 379 were treated with definitive radiation. Median follow-up was 32.6 months. After adjusting for age, location, insurance, income, and comorbidity index, radiation alone (REF: surgery alone; hazard ratio [HR]:1.73; 95% confidence interval (CI):1.17-2.53) and modified IB stage (REF: IA stage; HR 2.06; 95% CI:1.35-3.38) were associated with increased all-cause mortality.

Conclusions: The influence of select sociodemographic factors, comorbidity, modified AJCC stage, and treatment paradigm on overall mortality in HPV+ OPC patients undergoing unimodal therapy warrants further exploration. Favorable outcomes in the surgery alone cohort may provide a rationale for secondary prevention of HPV+ OPC. A screened population with very early (modified stage IA) disease may be eligible for de-escalated treatment and still achieve excellent oncologic outcomes.

Introduction, Methods, and Materials

- See abstract; additional exclusion criteria: prior or synchronous cancer, M1 disease, palliative treatment, absent diagnosis/staging/treatment data, radiation alone with > 11 lymph nodes examined
- AJCC 8th edition clinical stage I disease was modified using AJCC7 clinical nodal staging to distinguish a subcohort with very favorable tumor characteristics (modified AJCC8 clinical stage IA: cTx/cT0/cT1 and AJCC7 cN0/cN1/cN2a) from a subcohort with favorable tumor characteristics (modified AJCC8 clinical stage IB: cTx/cT0/cT1 and AJCC7 cN2b; cT2 and AJCC7 cN0/cN1/cN2a/cN2b; Figure 1).

Figure 1. Modified 8th Ed AJCC Staging System

			Tumor Staging				
Nodal Staging	AJCC 8 th Edition	AJCC 7 th Edition	AJCC 8 th Edition				
			cT0/Tx	cT1	cT2	cT3	cT4
	cN0	cN0	IA	IA	IB	II	III
	cN1	cN1	IA	IA	IB	II	III
	cN1	cN2a	IA	IA	IB	II	III
	cN1	cN2b	IB	IB	IB	II	III
	cN2	cN2c	II	II	II	II	III
	cN3	cN3	III	III	III	III	III

Results

Table 1: Demographic, Tumor and Treatment Characteristics

Variable	Surgery Alone (n= 697)	Radiation Alone (n=379)	p-value
Age (median, IQR)	59 (53-66)	61 (56-69)	<0.001
Location			0.01
West/Pacific	149 (21.4)	72 (19.0)	
New England/Mid-Atlantic	153 (22.0)	62 (16.4)	
South	184 (26.4)	134 (35.4)	
Midwest	211 (30.3)	111 (29.3)	
Income (\$)			0.019
>63,000	290 (41.6)	121 (31.9)	
48,000-62,999	181 (26.0)	114 (30.1)	
38,000-47,999	151 (21.7)	93 (24.5)	
<38,000	75 (10.8)	51 (13.5)	
Insurance			<0.001
Private insurance	441 (63.3)	184 (48.6)	
Not insured	15 (2.2)	10 (2.6)	
Medicaid	33 (4.7)	17 (4.5)	
Medicare	196 (28.1)	151 (39.8)	
Other Government	12 (1.7)	17 (4.5)	
Charlson Comorbidity Index			0.012
0	544 (78.1)	320 (84.4)	
1+	153 (22.0)	59 (15.6)	
Modified AJCC Stage 8 th Ed			<0.001
IA	310 (44.5)	72 (19.0)	
IB	333 (47.8)	242 (63.9)	
II	40 (5.7)	46 (12.1)	
III	14 (2.0)	19 (5.0)	
Months Follow-up (median, IQR)	33.6 (18.9-51.5)	31.0 (17.9-46.9)	0.17

Table 2: Adjusted Overall Mortality (aOM) Hazard Ratios

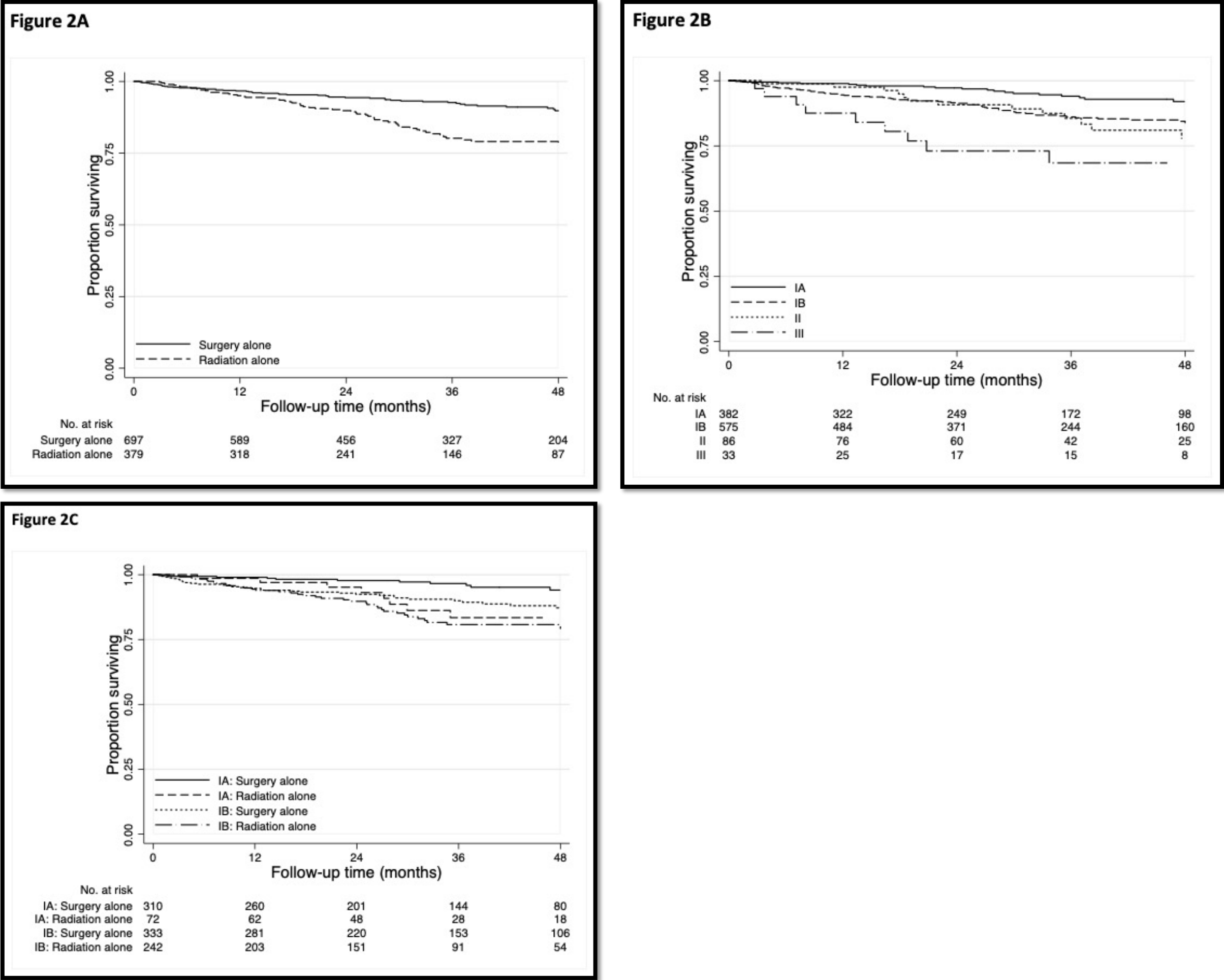
Variable	aOM Hazard Ratio	95% CI	p-value
Age	1.04	1.02-1.07	<0.001
Location			
West/Pacific	-		
New England, Mid-Atlantic	1.85	1.005-3.41	0.048
South	1.11	0.60-2.04	0.749
Midwest	1.67	0.96-2.93	0.069
Income (in dollars)			
>/= 63,000	-		
48,000-62,999	1.19	0.73-1.94	0.484
38,000-47,999	1.16	0.69-1.94	0.572
<38,000	2.28	1.32-3.95	0.003

Results

Table 2 (Continued): Adjusted Overall Mortality (aOM) Hazard Ratios

Variable	aOM Hazard Ratio	95% CI	p-value
Insurance			
Private insurance	-		
Not insured	3.09	1.17-8.16	0.023
Medicaid	2.23	0.99993-4.95	0.050
Medicare	1.97	1.19-3.27	0.008
Other Government	1.49	0.36-6.28	0.584
Charlson Comorbidity Index			
0	-		
1 or more	1.65	1.11-2.47	0.014
Modified AJCC Stage 8 th , Ed			
IA	-		
IB	2.06	1.25-3.38	0.004
II	1.86	0.93-3.73	0.079
III	4.34	1.97-9.55	<0.001
Unimodality Treatment			
Surgery alone	-		
Radiation alone	1.73	1.17-2.53	0.005

Figure 2: Kaplan-Meier Estimates of Overall Survival Stratified by Treatment and Modified AJCC 8th Ed Stage



Results

Figure 2A: Four-year overall survival (OS) rates: surgery alone (89.8%; 95% CI: 86.5-92.3%); radiation alone (78.1%; 95% CI: 72.3-82.9%; p<0.001)

Figure 2B: Four-year OS rates: modified stage IA patients (92.0%; 95% CI: 87.4-95.0%; modified stage IB patients (83.9%; 95% CI: 79.8-87.3%); stage II patients (77.9%; 95%: 63.9-87.0%); stage III patients (68.5%; 95% CI: 47.6-82.4%).

Figure 2C: Four-year OS rates: modified AJCC 8th edition stage IA patients (94.1%; 95% CI: 89.0-96.8%); radiation alone (83.4%; 95% CI: 69.1-91.5%). Four-year OS rates: modified AJCC 8th edition stage IB patients who underwent surgery alone (87.2%; 95% CI: 82.1-91.0%); radiation alone (79.3%; 95% CI: 71.8-85.0%).

Discussion

- On adjusted analyses, radiation alone (REF: surgery alone) and modified stage IB (REF: modified stage IA) significantly predicted for increased overall mortality.
 - The etiology of superior outcomes associated with surgery alone is uncertain. Other studies evaluating multimodal therapy in these patients have failed to ascertain a difference in outcomes according to treatment paradigm.
- Among HPV+ OPC patients undergoing unimodal therapy, our findings argue for adoption of a modified staging system that subcategorizes AJCC 8th edition stage I patients into subgroups with distinct clinical outcomes.
- Exploration of the adjusted associations between location, insurance, income and comorbidity with overall mortality in this population is also indicated.
- Considering the 94% four-year OS of modified stage IA HPV+ OPC patients treated with surgery alone, our findings compellingly advocate for the advancement of HPV+ OPC screening.
 - Early detection of modified stage IA disease may facilitate meaningful treatment de-escalation with surgery alone while preserving excellent oncologic outcomes in this population.
- The National Cancer Database exhibits important limitations as it does not incorporate recurrence data and does not account for important exposures such as tobacco dependence, alcohol use, and perineural invasion.
 - Therefore, validation studies using institutional- and other national database data will be necessary to corroborate or refute the external validity of this data.

Conclusions

- Among HPV+ OPC patients undergoing unimodal therapy, favorable outcomes in the following patients warrant further exploration:
 - Surgery alone (versus radiation alone)
 - Modified AJCC 8th edition overall stage IA (versus modified AJCC 8th edition overall stage IB)
- Considering the excellent outcomes of very early-stage patients undergoing unimodality therapy with surgery alone, our data strongly support exploration of the utility of screening for HPV+ OPC.

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