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Derivation and validation of the AJCC9V pathological stage classification for HPV-positive oropharyngeal carcinoma: a multicentre registry analysis

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Introduction

Human papillomavirus (HPV)

- **Prevalence:** 45% of all head and neck malignancies in USA
- **Dominance:** 80% of all OPSCC (Oropharyngeal Squamous Cell Carcinoma) cases in USA
- **Comparison:** Incidence of HPV-positive oropharyngeal carcinoma has overtaken that of cervical cancer in several countries
- **Prognosis:** HPV-positive oropharyngeal carcinoma imparts a mortality risk two to three times lower than that of HPV-negative oropharyngeal carcinoma

AJCC8E Major Achievements

- Recognising HPV-positive oropharyngeal carcinoma as a distinct entity
- Reserving Stage IV exclusively for M1 disease
- Streamlining nodal determinants of prognosis

	AJCC7E	AJCC8E	AJCC9V
pN classification			
N0	0 positive lymph nodes	0 positive lymph nodes	0 positive lymph nodes
N1	1 positive lymph node (≤3 cm)	1–4 positive lymph nodes	..
N1a	..	..	1 positive lymph node and ENE-negative
N1b	..	..	2–4 positive lymph nodes and ENE-negative
N2	..	>4 positive lymph nodes	1–4 positive lymph nodes and ENE-positive >4 positive lymph nodes and ENE-negative
N2a	1 positive lymph node (3–6 cm)	..	..
N2b	>1 positive lymph nodes (≤6 cm)	..	..
N2c	>1 positive lymph nodes (bilateral or contralateral; ≤6 cm)	..	..
N3	≥1 positive lymph nodes (>6 cm)	..	>4 positive lymph nodes and ENE-positive
pTNM stage			
Stage I	T1N0M0	T0-2N0-1M0	T0-2N0-1M0
Stage II	T2N0M0	T0-2N2M0 T3-4N0-1M0	T0-2N2-3M0 T3N0-2M0
Stage III	T3N0M0 T1-3N1M0	T3-4N2M0	T3N3M0 T4N0-3M0
Stage IV	..	M1	M1
Stage IVA	T4aN0-2M0 T1-3N2M0	..	..
Stage IVB	T4bM0 T1-T4N3M0	..	..
Stage IVC	M1	..	..

AJCC7E=American Joint Committee on Cancer staging system, 7th edition. AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9. ENE=extranodal extension. HPV=human papillomavirus.

Table 2: **Comparison of pathological N classification and TNM stage for HPV-positive oropharyngeal carcinoma**

AJCC8E Emerging Imbalances

- One-sided distribution
  - pN classification (>85% of cases are N1)
  - stage groupings (>80% of cases are Stage I) → poor risk stratification
- Misalignment between staging and treatment decisions
  - T1N1 patients receive highly variable post-operative management (observation vs RT vs CRT)
- Absent extranodal extension (ENE), which gained prominence in trial design and clinical practice

Methods

Study design

- AJCC Expert Panel met over 4 months with three rounds of data iteration to achieve consensus
- Data were abstracted from the National Cancer Database (NCDB) from 2010~2019
- **Inclusion** criteria: All patients aged older than 18 years who underwent upfront surgical resection with neck dissection (minimum ten lymph nodes examined) for HPV-positive oropharyngeal carcinoma for curative intent
- Data were dichotomised into derivation (west, midwest) and validation (east, south) cohorts

Study design – NCDB encoded pENE

- 2010 to 2017
  - pENE-negative
  - pENE-positive microscopic
  - pENE-positive macroscopic
  - pENE-positive NOS (not otherwise specified)
- 2018 to 2019
  - Microscopic: 2 mm or smaller
  - Macroscopic: greater than 2 mm
- This study described pENE-positive as any pENE positivity (2010–19)
- Subset analyses: pENE-positive minor as up to 2 mm and major as greater than 2 mm (2018–19)

Outcomes

- **Objectives**: To derive and validate an optimised HPV-positive OPSCC pathological staging classification based on overall survival (OS)
- Adjusted hazard ratio (AHR) data in conjunction with clinical considerations were used to formulate an optimal staging schema

Statistical analysis

1. Multivariable Cox proportional hazards regression model on **overall survival**
   - pENE-positive vs pENE-negative
   - pENE-positive minor vs major vs pENE-negative
2. **Restricted Cubic Splines**: non-linear association between metastatic lymph node count and survival
3. Optimal classification: Adjusted hazard ratios (AHRs) + Recursive Partitioning Analysis (RPA)
4. **Staging** classification: AHRs for mortality risk for all T and N combinations within the derivation cohort, to derive Stage I–III schema, then tested on a validation cohort
5. **Groome's Criteria**: evaluate performance

Results

Derivation & Validation Cohorts

Total Patients: 14447 across 984 facilities, between 2010 and 2019

7,768

Derivation Cohort
(West & Midwest US)

6,679

Validation Cohort
(East & South US)

Patient Characteristics

Sex

85.0% Male

15.0% Female

Race

94.1% White

3.4% Black

2.5% Other

Median Follow-up

52.4 months

(95% CI 51.5–53.3)

Pathological Features

- Lymph Node Yield
  - **Median Nodes Examined:** 31 (IQR 22–42)
  - **Mean Positive Nodes:** 2.5 (SD 3.6)
- Extranodal Extension
  - **pENE Prevalence:** 31.5% (4,552 / 14,447 patients).

Statistical analysis

1. Multivariable Cox proportional hazards regression model on **overall survival**
   - pENE-positive vs pENE-negative
   - pENE-positive minor vs major vs pENE-negative

Non-Nodal Determinants of prognosis

Multivariable analysis identified independent factors associated with increased mortality risk:

Factor	Hazard Ratio (HR)	p-value
Advanced T-Stage (T4)	2.86 [2.32 - 3.52]	< 0.0001
Positive Margins	1.29 [1.14 - 1.45]	< 0.0001
Lymphovascular Invasion (LVI)	1.35 [1.20 - 1.50]	< 0.0001

Extranodal Extension (ENE)

- A Major Risk Factor
- **Survival Gap:** pENE-negative had significantly better 3-year OS (94.8%) [95% CI 94·3–95·3] compared to pENE-positive patients (89.7%) [88·8–90·7], p<0·0001)
- **Hazard Ratio:** Presence of pENE is independently associated with mortality (HR 1.47 [1.30–1.65], p<0.0001) on multivariable analysis

Minor vs. Major ENE

Using the 2018-2019 data (n=4,767) on multivariable analysis

ENE Category	Definition	Multivariable HR	p-value
pENE-Negative	None	1.0 (Reference)	-
pENE-Minor	≤ 2 mm	0.99 [0.63 - 1.55]	0.96
pENE-Major	> 2 mm	1.38 [0.85 - 2.26]	0.20

Finding: No significant prognostic difference between Minor and Major ENE

	pENE status (2010–19)		pENE extent (2018–19)	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1·03 (1·02–1·04)	<0·0001	1·04 (1·02–1·05)	<0·0001
Sex				
Male	..	..	..	..
Female	0·89 (0·77–1·03)	0·11	0·85 (0·60–1·21)	0·37
T stage				
T1	..	..	..	..
T2	1·29 (1·16–1·44)	<0·0001	1·00 (0·75–1·33)	0·98
T3	2·01 (1·69–2·39)	<0·0001	2·14 (1·40–3·29)	0·0005
T4	2·86 (2·32–3·52)	<0·0001	3·66 (2·13–6·29)	<0·0001
Number of metastatic lymph nodes	1·05 (1·04–1·05)	<0·0001	1·06 (1·04–1·08)	<0·0001
Margins				
Negative	..	..	..	..
Positive	1·29 (1·14–1·45)	<0·0001	1·57 (1·15–2·15)	0·0040
Postoperative radiotherapy				
No	..	..	..	..
Yes	0·66 (0·58–0·76)	<0·0001	0·55 (0·41–0·74)	<0·0001
Postoperative chemotherapy				
No	..	..	..	..
Yes	0·99 (0·87–1·13)	0·89	0·74 (0·51–1·08)	0·12
pENE status				
Negative	..	..	..	..
Positive	1·47 (1·30–1·65)	<0·0001	..	..
pENE extent				
Negative	..	..	..	..
Positive minor	..	..	0·99 (0·63–1·55)	0·96
Positive major	..	..	1·38 (0·85–2·26)	0·20

Multivariable Cox regression for overall survival stratified by pENE status (positive *vs* negative; 2010–19) and pENE extent (negative *vs* positive minor *vs* positive major; 2018–19). Covariates in the full models (appendix pp 9–12) included age, sex, race, tumour site, facility type, region, insurance status, median zip code income, proportion of adults in zip code with high school diploma, distance traveled to facility, Charlson-Deyo comorbidity score, T classification, number of lymph nodes examined, number of metastatic lymph nodes, metastatic lymph node size, lymphovascular invasion, pENE status, margins, postoperative radiotherapy, and postoperative chemotherapy. HPV=human papillomavirus. HR=hazard ratio. pENE=pathological extranodal extension.

Table 1: **Abridged multivariable analysis of overall survival for HPV-positive oropharyngeal carcinoma**

Statistical analysis

1. Multivariable Cox proportional hazards regression model on **overall survival**
   - pENE-positive vs pENE-negative
   - pENE-positive minor vs major vs pENE-negative
2. **Restricted Cubic Splines**: non-linear association between metastatic lymph node count and survival

Nodal Determinants of prognosis

- Increasing number of metastatic lymph nodes was significantly associated with worse overall survival on multivariable analysis
- Metastatic lymph node size was not associated with mortality

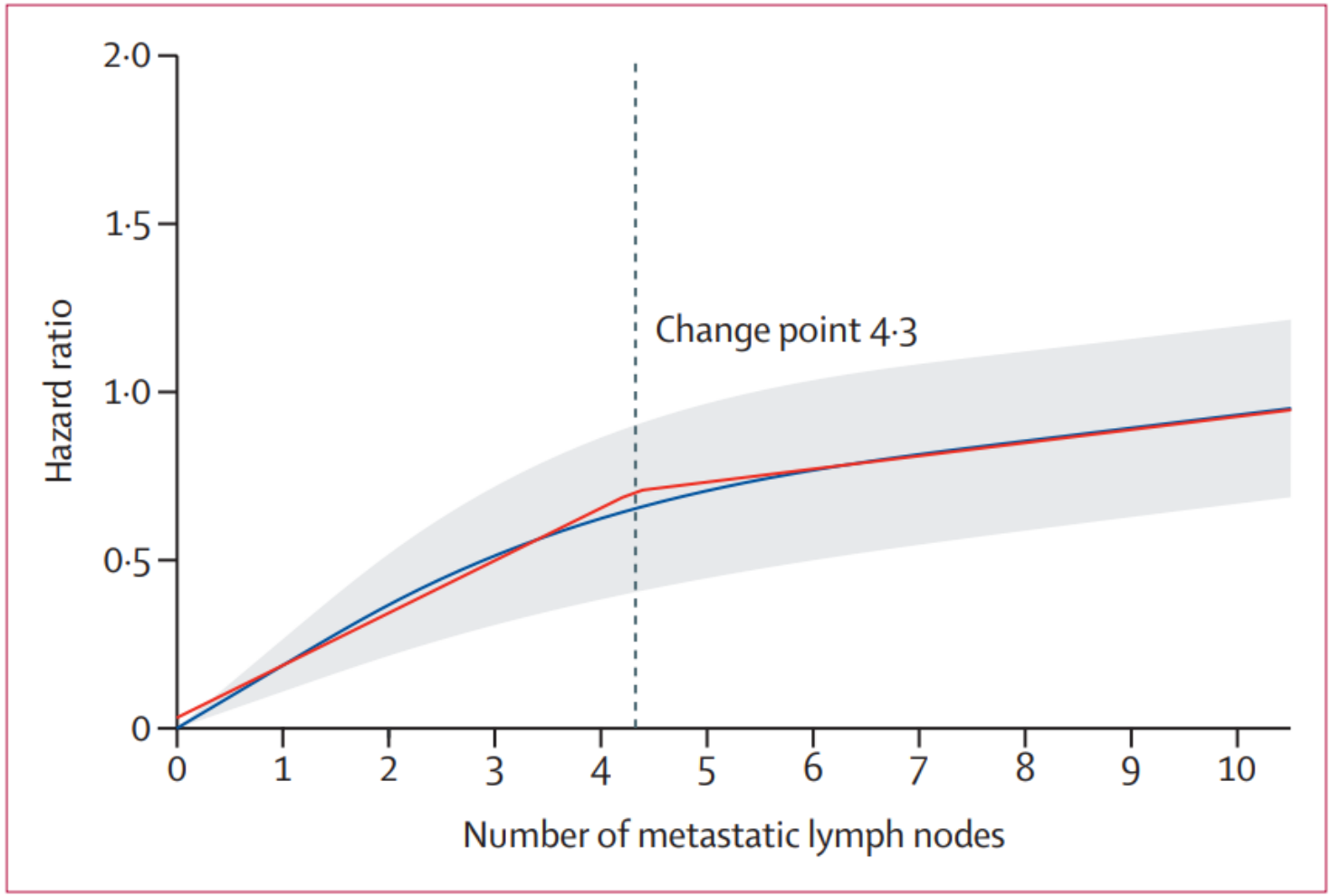

Figure 1: **Adjusted mortality risk with increasing number of metastatic lymph nodes in HPV-positive oropharyngeal carcinoma**

Using derivation data, regional metastatic lymph node was fit with a multivariable restricted cubic spline plot, illustrating adjusted hazard ratios with increasing number of metastatic lymph nodes for human papillomavirus (HPV)-positive oropharyngeal carcinoma. Three knots were placed at 1, 2, and 8 lymph nodes. The estimated change point was 4·3 metastatic lymph nodes.

The "4.3 Nodes" Threshold

4.3

Optimal Changepoint
(Number of Positive Nodes)

Below 4.3

Mortality risk **increases sharply** with each additional node.
HR 1.20 [1.11 - 1.29] per node.
($p < 0.0001$)

Above 4.3

Risk continues to increase but **plateauing**
HR 1.04 [1.02 - 1.06] per node.
($p < 0.0001$)

Conclusion: A cutoff of 4 nodes is statistically justified for staging.

Nodal Determinants of prognosis

- Cutoff of 4 positive lymph nodes served as the foundation for N categories
  - 1–4 positive lymph nodes **vs** >4 positive lymph nodes
- Cases with **1 positive** lymph node and ENE-negative
  - large proportion of cases
  - many patients undergo single-modality treatment
- Leading to three groups of lymph nodes
  - 1 positive
  - 2–4 positive
  - >4 positive

The Logic of Splitting N1

The Problem of AJCC8E

- **>85%** of patients as N1 (1-4 nodes)

The Solution of AJCC9V

- Splits this group based on two drivers:
  - **Node Count** (1 vs 2-4 vs >4)
  - **ENE Status** (Positive vs Negative)

Statistical analysis

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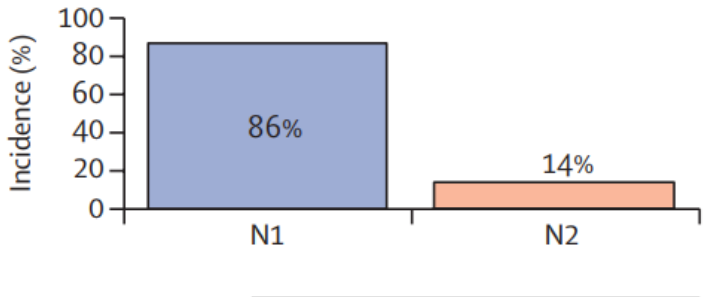
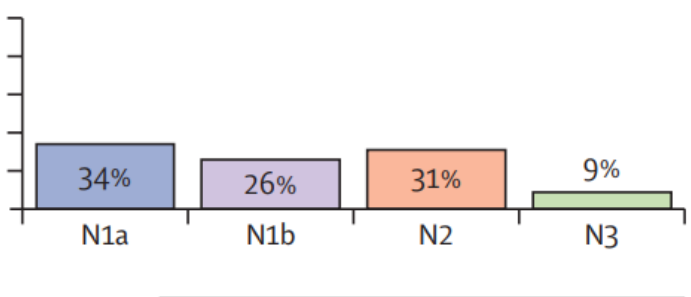
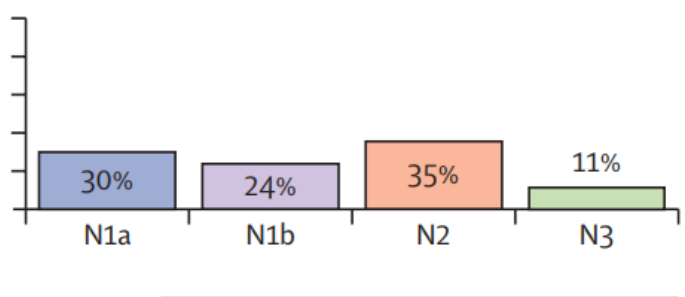
3. Optimal classification: Adjusted hazard ratios (AHRs) + Recursive Partitioning Analysis (RPA)



	1 LN+	2–4 LN+	>4 LN+
pENE-negative	N1 (n=2128); AHR 1 (ref)	N1 (n=1630); AHR 1·32	N2 (n=305); AHR 2·04
pENE-positive	N1 (n=698); AHR 1·85	N1 (n=942); AHR 1·45	N1 (n=571); AHR 3·36

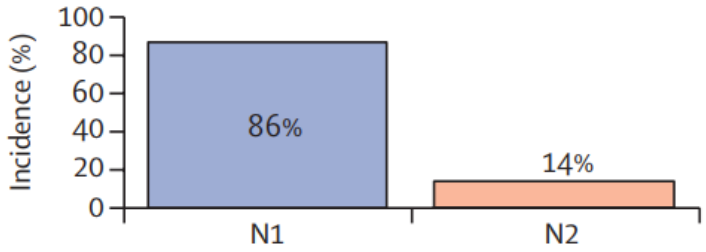


	1 LN+	2–4 LN+	>4 LN+
pENE-negative	N1a (n=2128); AHR 1 (ref)	N1b (n=1630); AHR 1·32	N2 (n=305); AHR 2·04
pENE-positive	N2 (n=698); AHR 1·85	N2 (n=942); AHR 1·45	N3 (n=571); AHR 3·36



	1 LN+	2–4 LN+	>4 LN+
pENE-negative	N1a (n=1645); AHR 1 (ref)	N1b (n=1313); AHR 1·54	N2 (n=236); AHR 2·14
pENE-positive	N2 (n=656); AHR 1·46	N2 (n=1053); AHR 2·44	N3 (n=627); AHR 3·59

Figure 2: **Generation of proposed AJCC9V pathological N classification for HPV-positive oropharyngeal carcinoma with Kaplan–Meier overall survival curves**
(A) AJCC8E pN classification (derivation cohort). (B) Proposed AJCC9V pN classification (derivation cohort). (C) Proposed AJCC9V pN classification (validation cohort). AHR=adjusted hazard ratio. AJCC7E=American Joint Committee on Cancer staging system, 7th edition. AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9. ENE=extranodal extension. HPV=human papillomavirus. LN+=positive lymph node.



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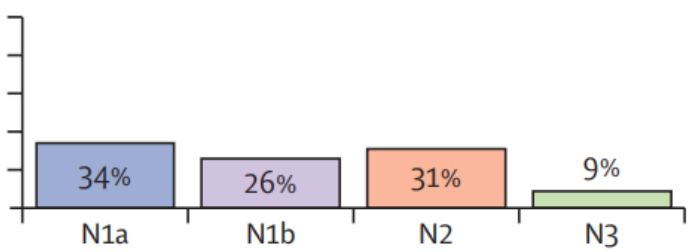

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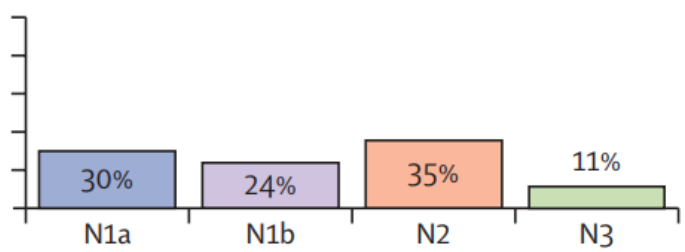

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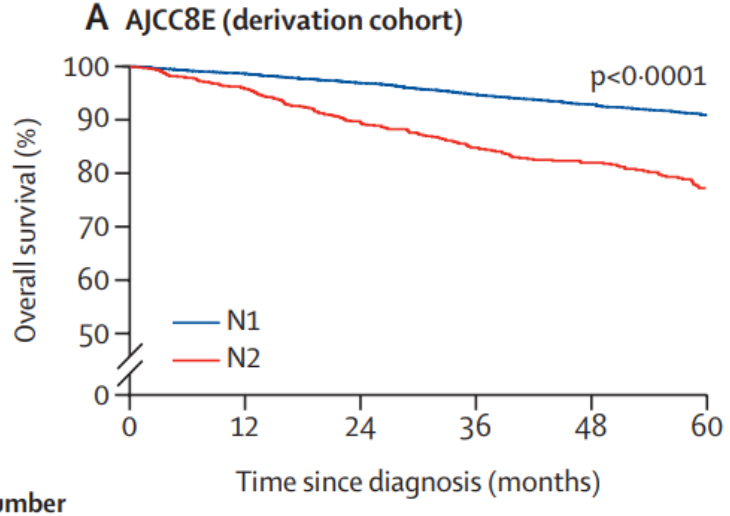
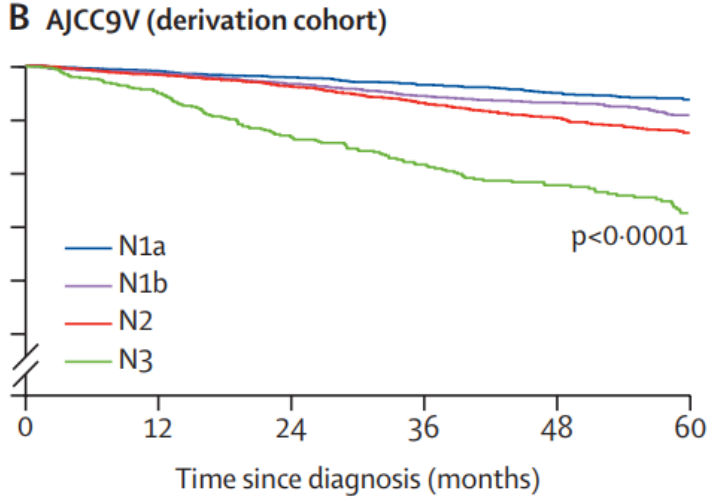
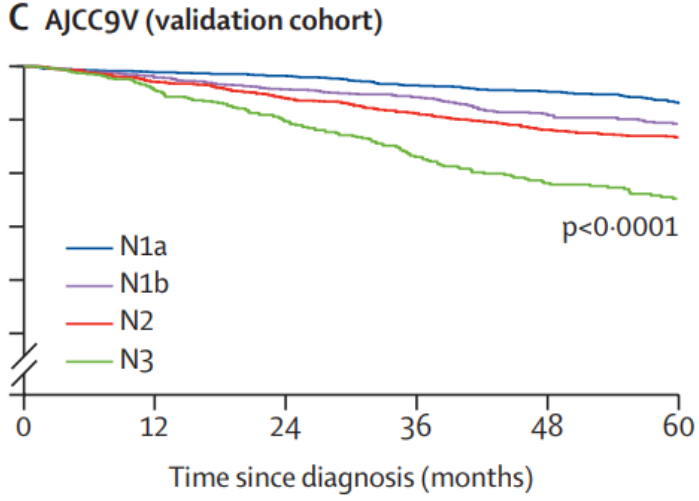
Discrepancy: 1 positive lymph node and ENE-positive (AHR 1·46)

- AHR value approximated the expected range
- Generally treated with postoperative CCRT, whereas N1b group are not

→ maintain N2 for clinical practicality







Number at risk (censored)						
N1	5718 (0)	5461 (180)	4848 (520)	3710 (1043)	2822 (827)	2048 (720)
N2	933 (0)	877 (17)	747 (73)	578 (135)	446 (116)	311 (111)

Number at risk (censored)												
N1a	2128 (0)	2030 (78)	1799 (207)	1404 (372)	1071 (315)	755 (306)	1645 (0)	1578 (49)	1414 (154)	1082 (309)	835 (236)	658 (159)
N1b	1630 (0)	1569 (39)	1376 (162)	1035 (313)	777 (247)	573 (186)	1313 (0)	1240 (46)	1084 (129)	841 (228)	642 (173)	573 (131)
N2	1945 (0)	1861 (51)	1669 (153)	1264 (358)	971 (261)	704 (238)	1945 (1)	1843 (46)	1636 (151)	1314 (277)	1055 (219)	842 (197)
N3	571 (0)	530 (12)	448 (37)	340 (85)	260 (67)	188 (55)	672 (0)	581 (18)	509 (38)	387 (88)	297 (69)	238 (49)

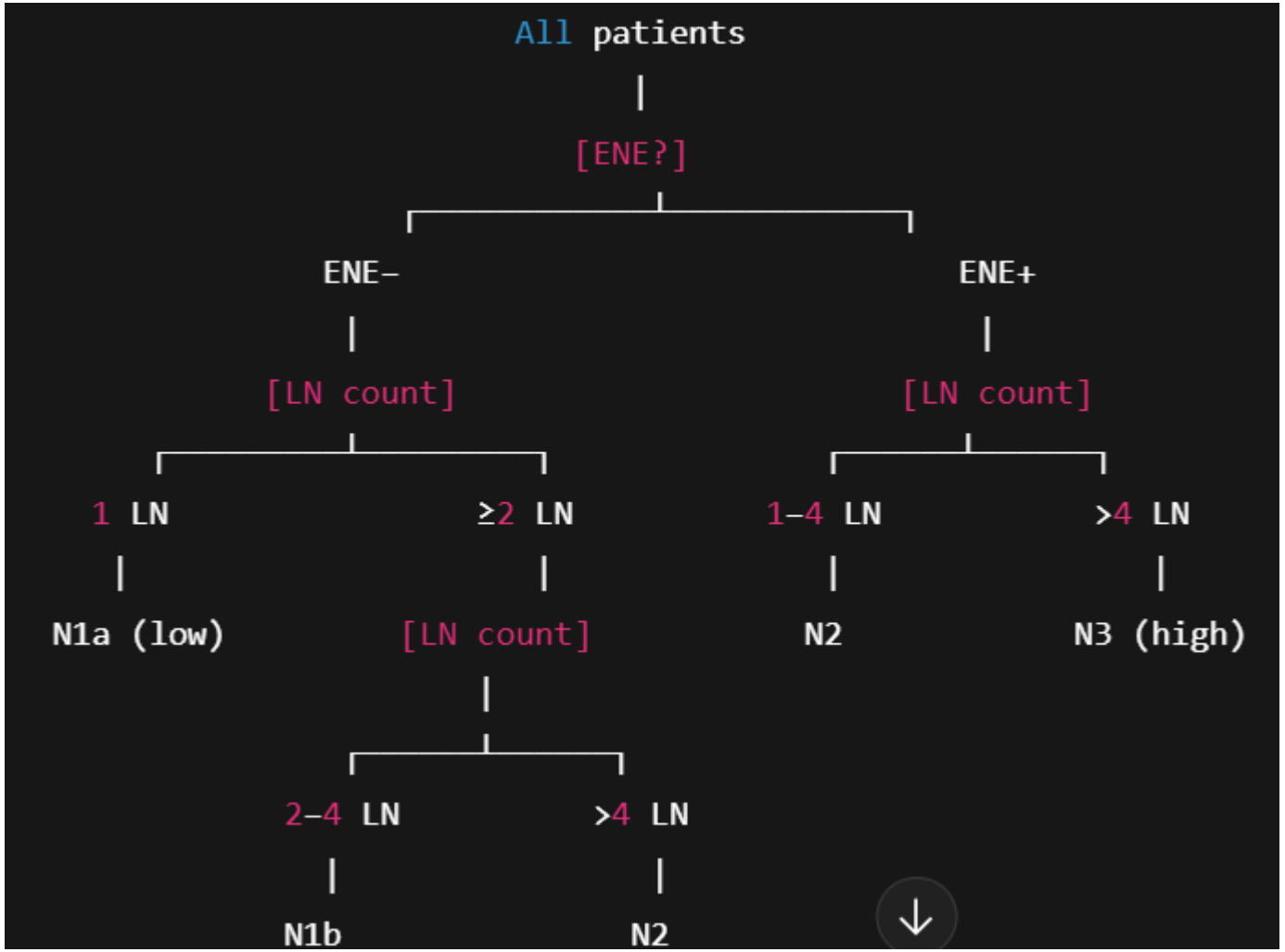
AJCC9V (derivation group) 5-year OS:

- 93·0% [95% CI 91·5–94·6] in N1a
- 89·3% [87·3–91·3] in N1b
- 86·7% [85·0–88·4] in N2
- 75·2% [71·5–79·2] in N3; p<0·0001

Recursive partitioning analysis (RPA)

- RPA identified multiple distinct clusters based on ENE and metastatic lymph node number
- Grouping of the clusters led to a nodal schema that mirrored and supported the AHR finding

Recursive partitioning analysis (RPA)



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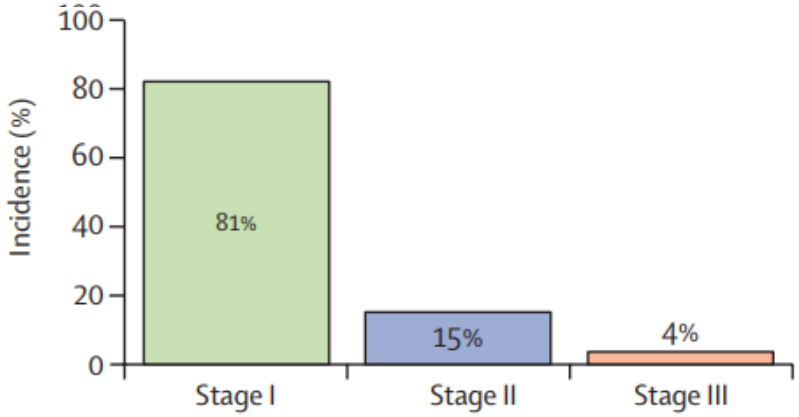
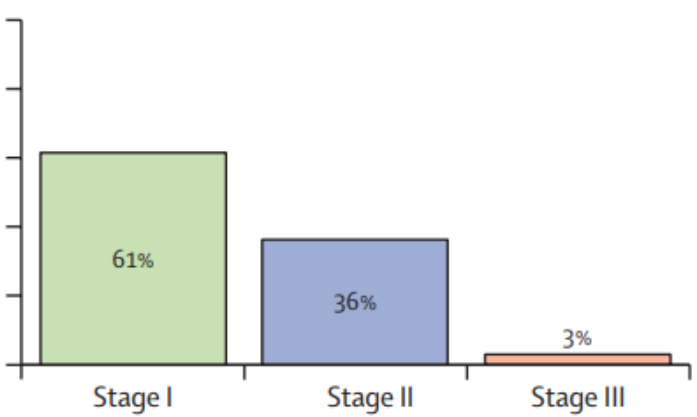
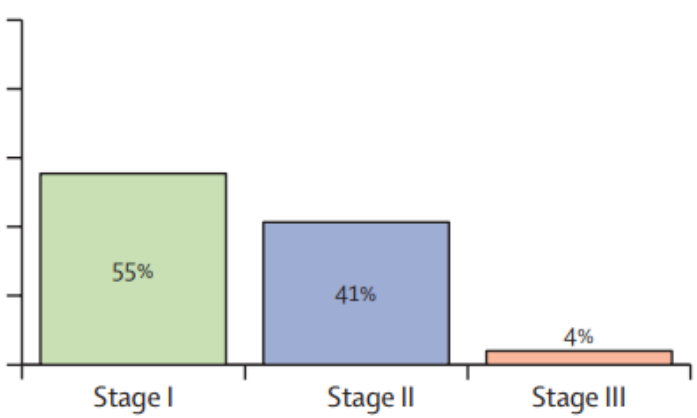


	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·5
pN1	I (n=3125) AHR 0·8	I (n=2231) AHR 1·2	II (n=262) AHR 2·2	III (n=100) AHR 2·3
pN2	II (n=423) AHR 2·1	II (n=368) AHR 2·3	III (n=82) AHR 2·7	III (n=60) AHR 4·4



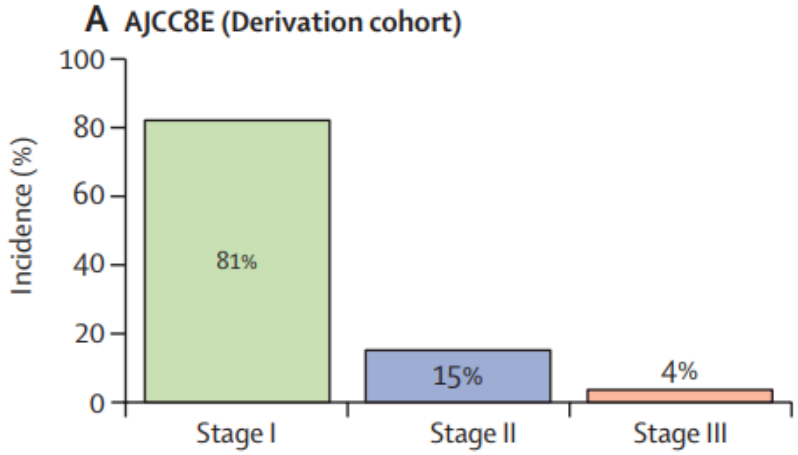
	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·7
pN1a	I (n=1292) AHR 0·7	I (n=839) AHR 0·9	II (n=106) AHR 1·7	III (n=28) AHR 2·3
pN1b	I (n=934) AHR 0·9	I (n=692) AHR 1·3	II (n=70) AHR 2·5	III (n=36) AHR 1·9
pN2	II (n=1054) AHR 1·1	II (n=826) AHR 1·9	II (n=117) AHR 2·9	III (n=46) AHR 3·2
pN3	II (n=297) AHR 2·9	II (n=243) AHR 2·8	III (n=53) AHR 3·8	III (n=48) AHR 5·4



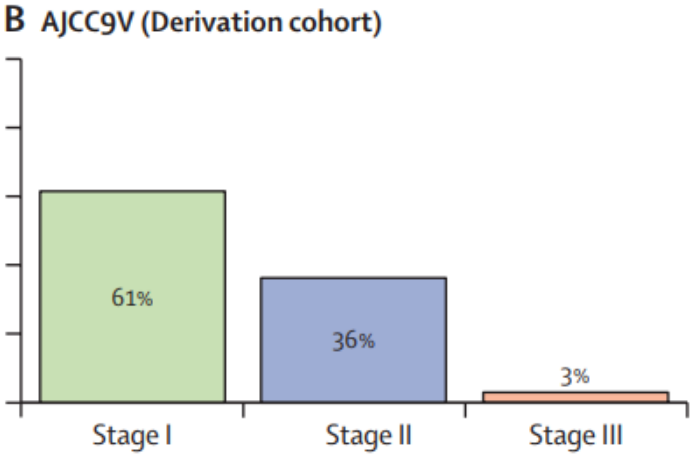
	pT0–T1	pT2	pT3	pT4
pN0	I (n=276) AHR 1 (ref)	I (n=474) AHR 1·1	II (n=87) AHR 2·2	III (n=36) AHR 5·5
pN1a	I (n=1010) AHR 1·0	I (n=652) AHR 1·2	II (n=76) AHR 1·8	III (n=9) AHR 3·0
pN1b	I (n=690) AHR 1·2	I (n=568) AHR 2·2	II (n=88) AHR 1·9	III (n=24) AHR 4·4
pN2	II (n=964) AHR 1·7	II (n=866) AHR 2·1	II (n=144) AHR 3·5	III (n=60) AHR 6·7
pN3	II (n=242) AHR 3·6	II (n=291) AHR 3·3	III (n=76) AHR 5·3	III (n=46) AHR 6·2

***Figure 3*: Generation of proposed AJCC9V pathological TNM staging for HPV-positive oropharyngeal carcinoma with associated Kaplan–Meier overall survival curves**

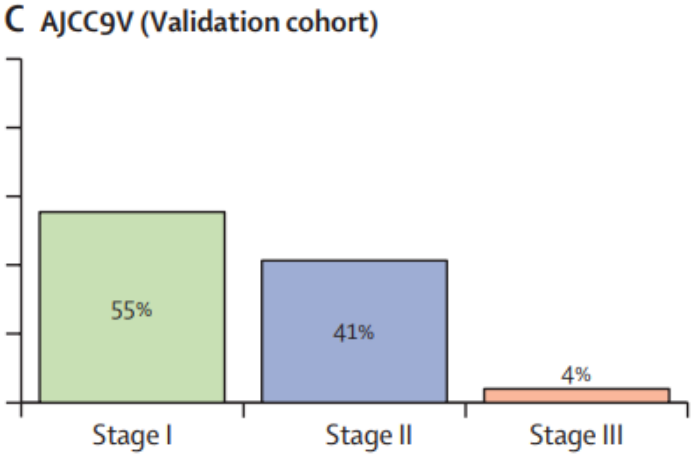
(A) AJCC8E pTNM (derivation cohort). (B) AJCC9V pTNM (derivation cohort). (C) AJCC9V pTNM (validation cohort). AHR=adjusted hazard ratio. AJCC7E=American Joint Committee on Cancer staging system, 7th edition. AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9. HPV=human papillomavirus.



	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·5
pN1	I (n=3125) AHR 0·8	I (n=2231) AHR 1·2	II (n=262) AHR 2·2	III (n=100) AHR 2·3
pN2	II (n=423) AHR 2·1	II (n=368) AHR 2·3	III (n=82) AHR 2·7	III (n=60) AHR 4·4



	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·7
pN1a	I (n=1292) AHR 0·7	I (n=839) AHR 0·9	II (n=106) AHR 1·7	III (n=28) AHR 2·3
pN1b	I (n=934) AHR 0·9	I (n=692) AHR 1·3	II (n=70) AHR 2·5	III (n=36) AHR 1·9
pN2	II (n=1054) AHR 1·1	II (n=826) AHR 1·9	II (n=117) AHR 2·9	III (n=46) AHR 3·2
pN3	II (n=297) AHR 2·9	II (n=243) AHR 2·8	III (n=53) AHR 3·8	III (n=48) AHR 5·4

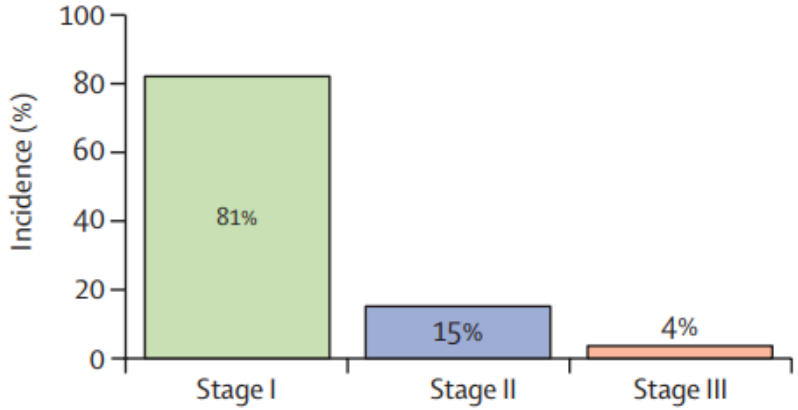


	pT0–T1	pT2	pT3	pT4
pN0	I (n=276) AHR 1 (ref)	I (n=474) AHR 1·1	II (n=87) AHR 2·2	III (n=36) AHR 5·5
pN1a	I (n=1010) AHR 1·0	I (n=652) AHR 1·2	II (n=76) AHR 1·8	III (n=9) AHR 3·0
pN1b	I (n=690) AHR 1·2	I (n=568) AHR 2·2	II (n=88) AHR 1·9	III (n=24) AHR 4·4
pN2	II (n=964) AHR 1·7	II (n=866) AHR 2·1	II (n=144) AHR 3·5	III (n=60) AHR 6·7
pN3	II (n=242) AHR 3·6	II (n=291) AHR 3·3	III (n=76) AHR 5·3	III (n=46) AHR 6·2

***Figure 3*: Generation of proposed AJCC9V pathological TNM staging for HPV-positive oropharyngeal carcinoma with associated Kaplan–Meier overall survival curves**

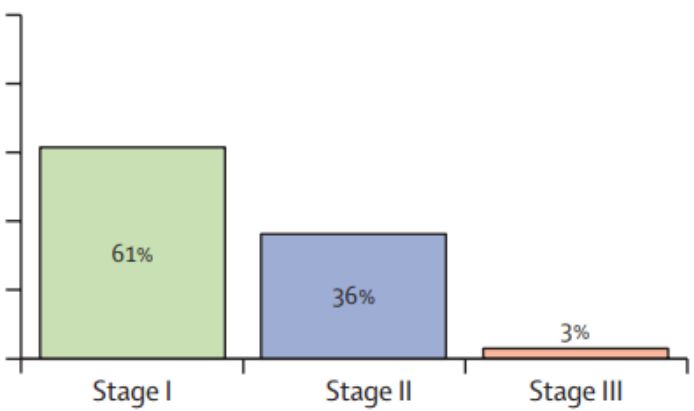
(A) AJCC8E pTNM (derivation cohort). (B) AJCC9V pTNM (derivation cohort). (C) AJCC9V pTNM (validation cohort). AHR=adjusted hazard ratio. AJCC7E=American Joint Committee on Cancer staging system, 7th edition. AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9. HPV=human papillomavirus.

A AJCC8E (Derivation cohort)



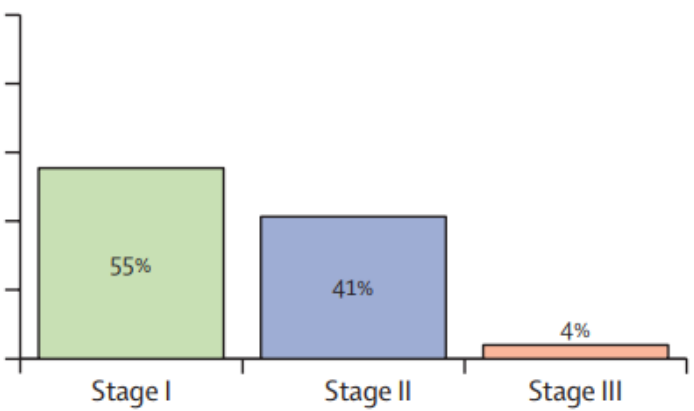
	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·5
pN1	I (n=3125) AHR 0·8	I (n=2231) AHR 1·2	II (n=262) AHR 2·2	III (n=100) AHR 2·3
pN2	II (n=423) AHR 2·1	II (n=368) AHR 2·3	III (n=82) AHR 2·7	III (n=60) AHR 4·4

B AJCC9V (Derivation cohort)



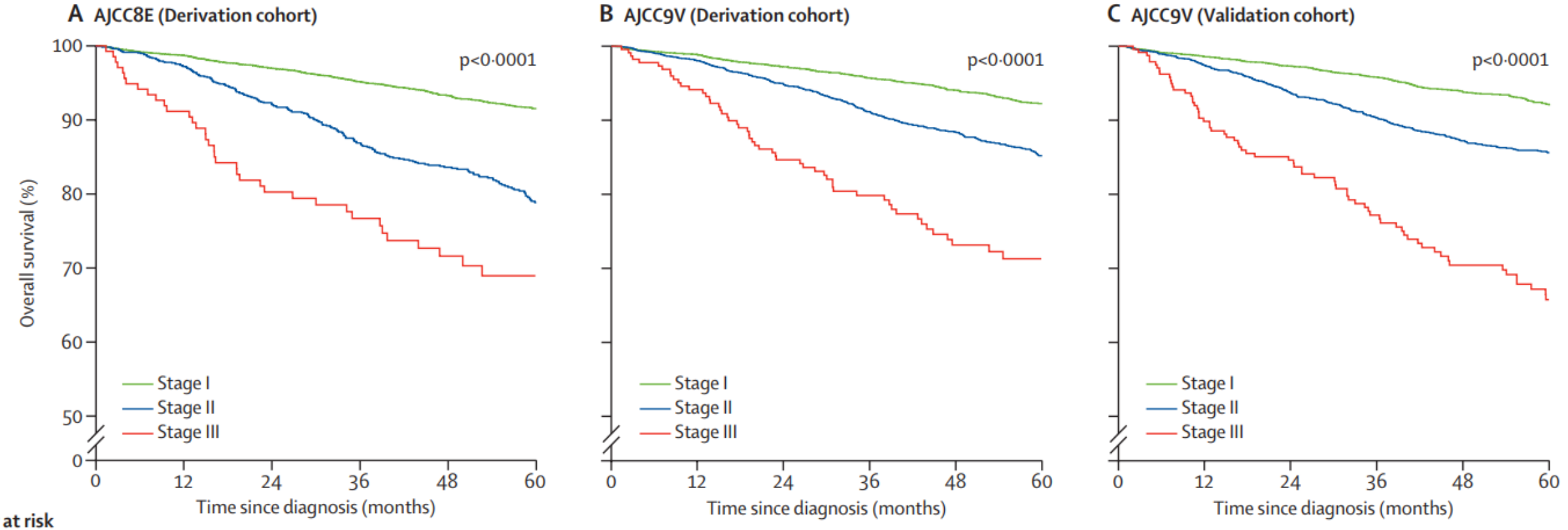
	pT0–T1	pT2	pT3	pT4
pN0	I (n=390) AHR 1 (ref)	I (n=581) AHR 1·0	II (n=109) AHR 1·5	III (n=37) AHR 3·7
pN1a	I (n=1292) AHR 0·7	I (n=839) AHR 0·9	II (n=106) AHR 1·7	III (n=28) AHR 2·3
pN1b	I (n=934) AHR 0·9	I (n=692) AHR 1·3	II (n=70) AHR 2·5	III (n=36) AHR 1·9
pN2	II (n=1054) AHR 1·1	II (n=826) AHR 1·9	II (n=117) AHR 2·9	III (n=46) AHR 3·2
pN3	II (n=297) AHR 2·9	II (n=243) AHR 2·8	III (n=53) AHR 3·8	III (n=48) AHR 5·4

C AJCC9V (Validation cohort)



	pT0–T1	pT2	pT3	pT4
pN0	I (n=276) AHR 1 (ref)	I (n=474) AHR 1·1	II (n=87) AHR 2·2	III (n=36) AHR 5·5
pN1a	I (n=1010) AHR 1·0	I (n=652) AHR 1·2	II (n=76) AHR 1·8	III (n=9) AHR 3·0
pN1b	I (n=690) AHR 1·2	I (n=568) AHR 2·2	II (n=88) AHR 1·9	III (n=24) AHR 4·4
pN2	II (n=964) AHR 1·7	II (n=866) AHR 2·1	II (n=144) AHR 3·5	III (n=60) AHR 6·7
pN3	II (n=242) AHR 3·6	II (n=291) AHR 3·3	III (n=76) AHR 5·3	III (n=46) AHR 6·2

Likely due to small numbers, as few T4 cases undergo surgery → maintain for clinical consistency



Number at risk (censored)																		
Stage I	6202	5915	5221	3974	2986	2166	4423	4222	3701	2821	2105	1509	3461	3291	2918	2246	1713	1333
	(0)	(208)	(595)	(1161)	(924)	(770)	(0)	(151)	(454)	(829)	(676)	(563)	(0)	(121)	(333)	(632)	(492)	(350)
Stage II	1272	1206	1044	797	619	434	2605	2487	2204	1666	1287	940	2595	2462	2173	1725	1366	1089
	(0)	(31)	(100)	(195)	(152)	(153)	(0)	(67)	(205)	(463)	(337)	(302)	(1)	(65)	(198)	(378)	(305)	(254)
Stage III	137	121	98	83	61	43	225	204	170	135	96	62	238	210	185	146	117	91
	(0)	(4)	(9)	(11)	(17)	(16)	(0)	(8)	(14)	(26)	(29)	(32)	(0)	(4)	(13)	(24)	(17)	(19)

AJCC9V (derivation group) 5-year OS:

- 92·3% [95% CI 91·3–93·2] in Stage I
- 85·2% [83·6–86·9] in Stage II
- 71·3% [64·9–78·4] in Stage III; p<0·001

	AJCC7E	AJCC8E	AJCC9V
pN classification			
N0	0 positive lymph nodes	0 positive lymph nodes	0 positive lymph nodes
N1	1 positive lymph node (≤3 cm)	1–4 positive lymph nodes	..
N1a	..	..	1 positive lymph node and ENE-negative
N1b	..	..	2–4 positive lymph nodes and ENE-negative
N2	..	>4 positive lymph nodes	1–4 positive lymph nodes and ENE-positive >4 positive lymph nodes and ENE-negative
N2a	1 positive lymph node (3–6 cm)	..	..
N2b	>1 positive lymph nodes (≤6 cm)	..	..
N2c	>1 positive lymph nodes (bilateral or contralateral; ≤6 cm)	..	..
N3	≥1 positive lymph nodes (>6 cm)	..	>4 positive lymph nodes and ENE-positive
pTNM stage			
Stage I	T1N0M0	T0-2N0-1M0	T0-2N0-1M0
Stage II	T2N0M0	T0-2N2M0 T3-4N0-1M0	T0-2N2-3M0 T3N0-2M0
Stage III	T3N0M0 T1-3N1M0	T3-4N2M0	T3N3M0 T4N0-3M0
Stage IV	..	M1	M1
Stage IVA	T4aN0-2M0 T1-3N2M0	..	..
Stage IVB	T4bM0 T1-T4N3M0	..	..
Stage IVC	M1	..	..

AJCC7E=American Joint Committee on Cancer staging system, 7th edition. AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9. ENE=extranodal extension. HPV=human papillomavirus.

Table 2: **Comparison of pathological N classification and TNM stage for HPV-positive oropharyngeal carcinoma**

Statistical analysis

1. Multivariable Cox proportional hazards regression model on **overall survival**
   - pENE-positive vs pENE-negative
   - pENE-positive minor vs major vs pENE-negative
2. **Restricted Cubic Splines**: non-linear association between metastatic lymph node count and survival
3. Optimal classification: Adjusted hazard ratios (AHRs) + Recursive Partitioning Analysis (RPA)
4. **Staging** classification: AHRs for mortality risk for all T and N combinations within the derivation cohort, to derive Stage I–III schema, then tested on a validation cohort
5. **Groome's Criteria**: evaluate performance (Hazard Consistency, Discrimination, Balance)

	Derivation cohort		Validation cohort		Combined cohort	
	AJCC8E	AJCC9V	AJCC8E	AJCC9V	AJCC8E	AJCC9V
Hazard consistency						
Score	2·81	2·65	2·84	2·15	4·92	4·15
Standardised score	1·00	0·00	1·00	0·00	1·00	0·00
Rank	2	1	2	1	2	1
Hazard discrimination						
Score	1·63	0·37	0·12	3·41	0·48	0·93
Standardised score	1·00	0·00	0·00	1·00	0·00	1·00
Rank	2	1	1	2	1	2
Likelihood difference						
Score	42·06	44·02	45·12	53·81	87·82	97·49
Standardised score	1·00	0·00	1·00	0·00	1·00	0·00
Rank	2	1	2	1	2	1
Explained variance						
Score	20·12	22·71	9·95	10·50	12·64	13·50
Standardised score	1·00	0·00	1·00	0·00	1·00	0·00
Rank	2	1	2	1	2	1
Balance						
Score	0·96	0·73	0·91	0·62	0·94	0·68
Standardised score	1·00	0·00	1·00	0·00	1·00	0·00
Rank	2	1	2	1	2	1
Overall rank						
Overall score	5·00	0·00	4·00	1·00	4·00	1·00
Rank	2	1	2	1	2	1
Performance						
Brier score	0·037	0·037	0·041	0·041	0·039	0·039
C-index	0·706	0·708	0·702	0·705	0·703	0·705

AJCC8E=American Joint Committee on Cancer staging system, 8th edition. AJCC9V=American Joint Committee on Cancer staging system, version 9.

Table 3: **Groome's criteria comparison of AJCC8E and AJCC9V pathological TNM staging schema**

Discussion

N1 cases reclassified into N1a, N1b

- **N1a (1 LN +, ENE −):** Commonly treated with surgery alone
- **N1b (2–4 LN +, ENE −):** Frequently treated with surgery followed by radiotherapy

Clinical implication:

- A **stepwise deterioration in survival** was observed from N1a to N1b
- Supports the clinical relevance of subdividing N1 disease

ENE

- Major risk factor meriting adjuvant CCRT across head and neck cancers
- ENE's **absence** of effect in earlier studies may stem from
  - Higher survival rates inherent to HPV-positive disease, which require greater numbers to power differences in outcome
  - Prognostic impact may be attenuated by systemic therapy in ENE-positive cases
  - Surgical cohorts often exclude advanced or gross ENE cases

→ Present findings may **underestimate the true prognostic effect of ENE**

ENE

- **Current limitation**: Pathological criteria for minor vs major ENE are underdeveloped with interrater variability
- **Future**: With refined pathology and longer follow-up, prognostic differences by ENE extent may emerge
- Recurrence rates remain substantial (10–25%), with poor outcomes after recurrence (2-yr OS ~55%) for HPV-positive OPSCC

Study Limitations

Retrospective

Registry-based retrospective design with potential coding errors

US-Centric

US-only cohort, predominantly White and male

Testing Variation

Non-uniform HPV testing across institutions

HPV and p16

- **p16: surrogate marker** for transcriptionally active high-risk HPV
- Not infallible
  - 10.9% of p16-positive cases are HPV-negative
  - 7.5% of p16-negative cases are HPV-positive
- College of American Pathologists recommends additional HPV testing in:
  - regions with low HPV-positive OPSCC prevalence
  - cases with equivocal p16 staining

Conclusion

Take home message

- Metastatic LN number and ENE are dominant prognostic factors
- AJCC9V
  - Improve hazard consistency within stages
  - Better inter-stage balance
  - Align staging more closely with treatment patterns

	AJCC8E	AJCC9V
pN classification		
N0	0 positive lymph nodes	0 positive lymph nodes
N1	1–4 positive lymph nodes	..
N1a	..	1 positive lymph node and ENE-negative
N1b	..	2–4 positive lymph nodes and ENE-negative
N2	>4 positive lymph nodes	1–4 positive lymph nodes and ENE-positive >4 positive lymph nodes and ENE-negative
N2a	..	..
N2b	..	..
N2c	..	..
N3	..	>4 positive lymph nodes and ENE-positive
pTNM stage		
Stage I	T0-2N0-1M0	T0-2N0-1M0
Stage II	T0-2N2M0 T3-4N0-1M0	T0-2N2-3M0 T3N0-2M0
Stage III	T3-4N2M0	T3N3M0 T4N0-3M0
Stage IV	M1	M1
Stage IVA	..	..
Stage IVB	..	..
Stage IVC	..	..

Thanks for your attention!