

CS Journal Reading

- Proposed Modification of Nodal Status in AJCC Esophageal Cancer Staging System

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Purpose

- Propose an modified nodal staging system to improve current American Joint Committee on Cancer (AJCC) esophageal cancer staging

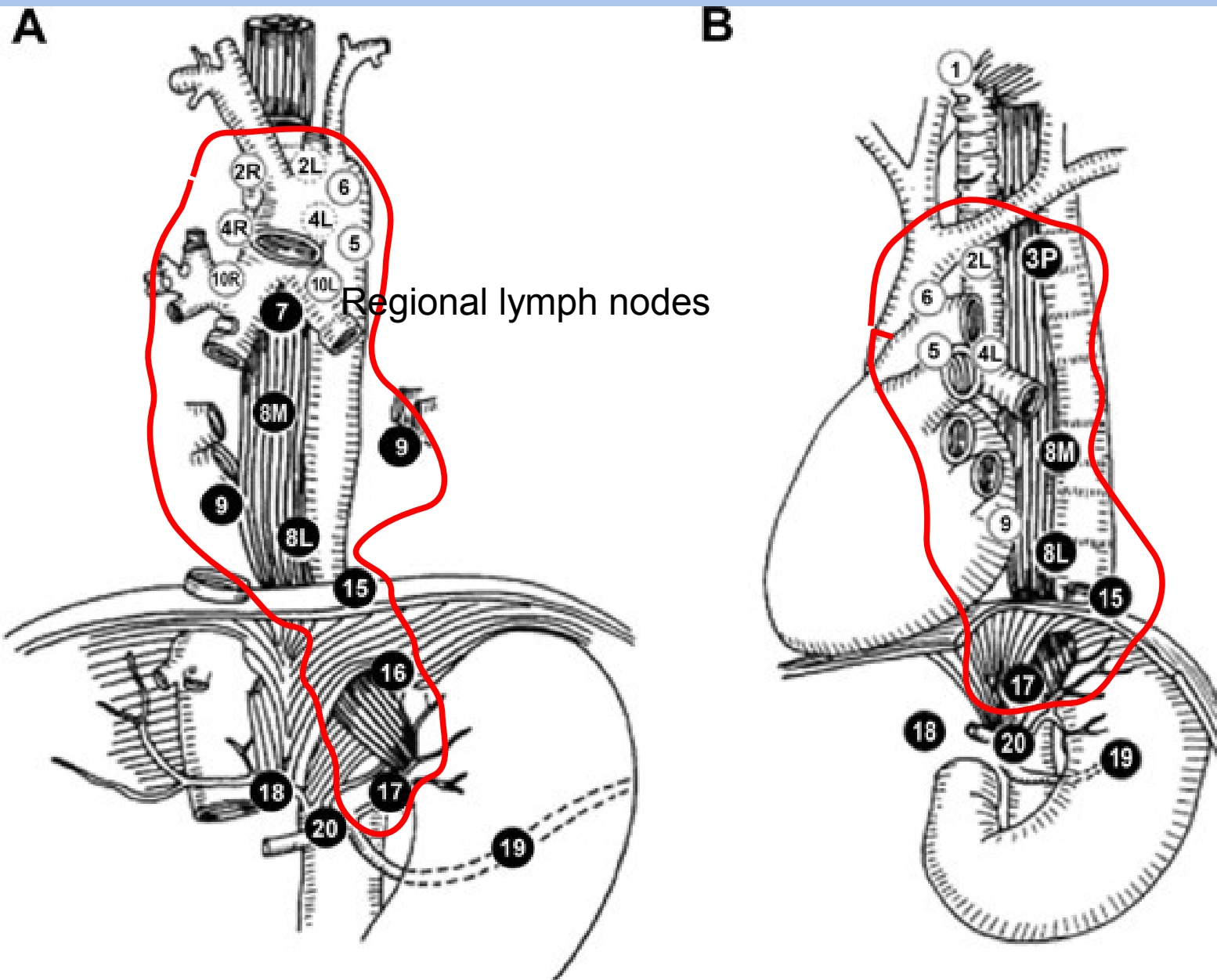
Current pTNM Staging System

- Primary tumor (T)
 - Tx Primary tumor cannot be assessed
 - T0 No evidence of primary tumor
 - Tis Carcinoma in situ
 - T1 Tumor invades lamina propria or submucosa
 - T2 Tumor invades muscularis propria
 - T3 Tumor invades adventitia
 - T4 Tumor invades adjacent structures

Current pTNM Staging System

- Regional lymph nodes (N)
 - Nx Regional nodes cannot be assessed
 - N0 No regional node metastasis
 - N1 Regional node metastasis
- Distant metastasis (M)
 - Mx Distant mets cannot be assessed
 - M0 No distant metastasis
 - M1a Celiac node metastasis for tumors of the lower esophagus/GEJ, supraclavicular node metastasis for tumors of the upper esophagus
 - M1b Nonregional nodal metastasis or distant metastasis

Current Nodal System



Drawbacks of Current System

- Difficult to interpret
- Based solely on lymph node location relative to the primary tumor's esophageal location
- Recent reports suggest that the number of lymph nodes involved is also an important factor

Methods

- 1,027 patients with resected esophageal cancer from 1970 to 2005 were reviewed
- Lymph nodes stations were assigned according to AJCC criteria
- Overall survival was assessed by Kaplan-Meier analysis
- The impact of location, number of involved lymph nodes, and use of preoperative C/T or R/T, or both, was assessed

Patient Selection - Inclusion

- Inclusion Criteria:
 - Histologically confirmed invasive SCC or adenocarcinoma of the esophagus and gastroesophageal junction
 - Number of resected lymph nodes should ≥ 4
- 1,027 patients were included
 - Neoadjuvant therapy: 595
 - Surgery alone: 432

Patient Selection - Exclusion

- Exclusion Criteria:
 - Recurrent cancer after nonsurgical therapy with pathologic complete response and observation
 - Limited high-grade dysplasia
 - Not survive longer than 30 days

Patient & Methods

- Preoperative Staging and Treatment
 - Locally advanced disease were treated with neoadjuvant therapy
 - Preoperative chemotherapy: 5-FU-based, platinum-based, and Taxol-based
 - Radiation treatment was given to 45 or 50.4 Gy over a 4- to 6-week period and administered with concurrent chemotherapy
- Lymph Node Station Designation
 - Lymph nodes were assigned a station designation according to the AJCC criteria

Patient Characteristics

Table 1. Patient Characteristics

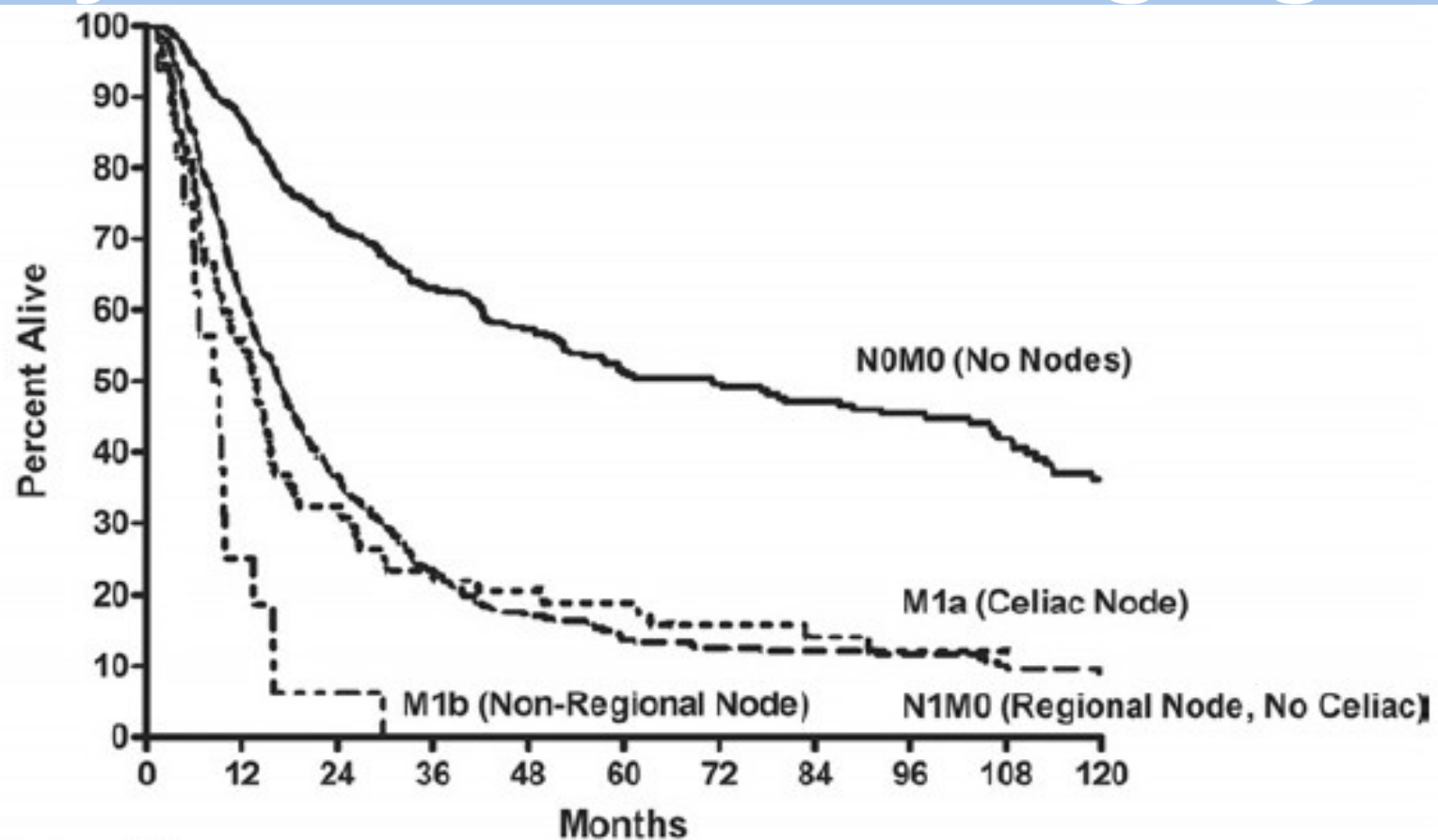
Demographics	(n = 1,027)
Age (median, range)	61 (34–79)
Sex	
Male	857 (83%)
Female	170 (17%)
Histology	
Adenocarcinoma	766 (75%)
Squamous cell carcinoma	261 (25%)
Location	
Cervical/upper	54 (5%)
Middle	153 (15%)
Lower/GEJ	820 (80%)
Pathologic stage	
0 ^a	136 (13%)
I	127 (12%)
IIA	223 (22%)
IIB	118 (12%)
III	324 (32%)
IVA	60 (6%)
IVB	39 (4%)
Lymph nodes involved	
0	496 (49%)
1–3	299 (29%)
> 3	232 (22%)

^a No viable tumor in the esophagus after induction therapy (T0).

GEJ = gastroesophageal junction.

- Vast majority were male with adenocarcinoma of the distal esophagus or gastroesophageal junction
- Pathologic downstaging after neoadjuvant therapy resulted in a significant number of patients achieving a pTNM stage 0
- Unsuspected M1b disease discovered at the time of surgery resulted in a stage IVb designation in 39 patients

Kaplan-Meier Survival – By Current AJCC Staging



Patients at risk:

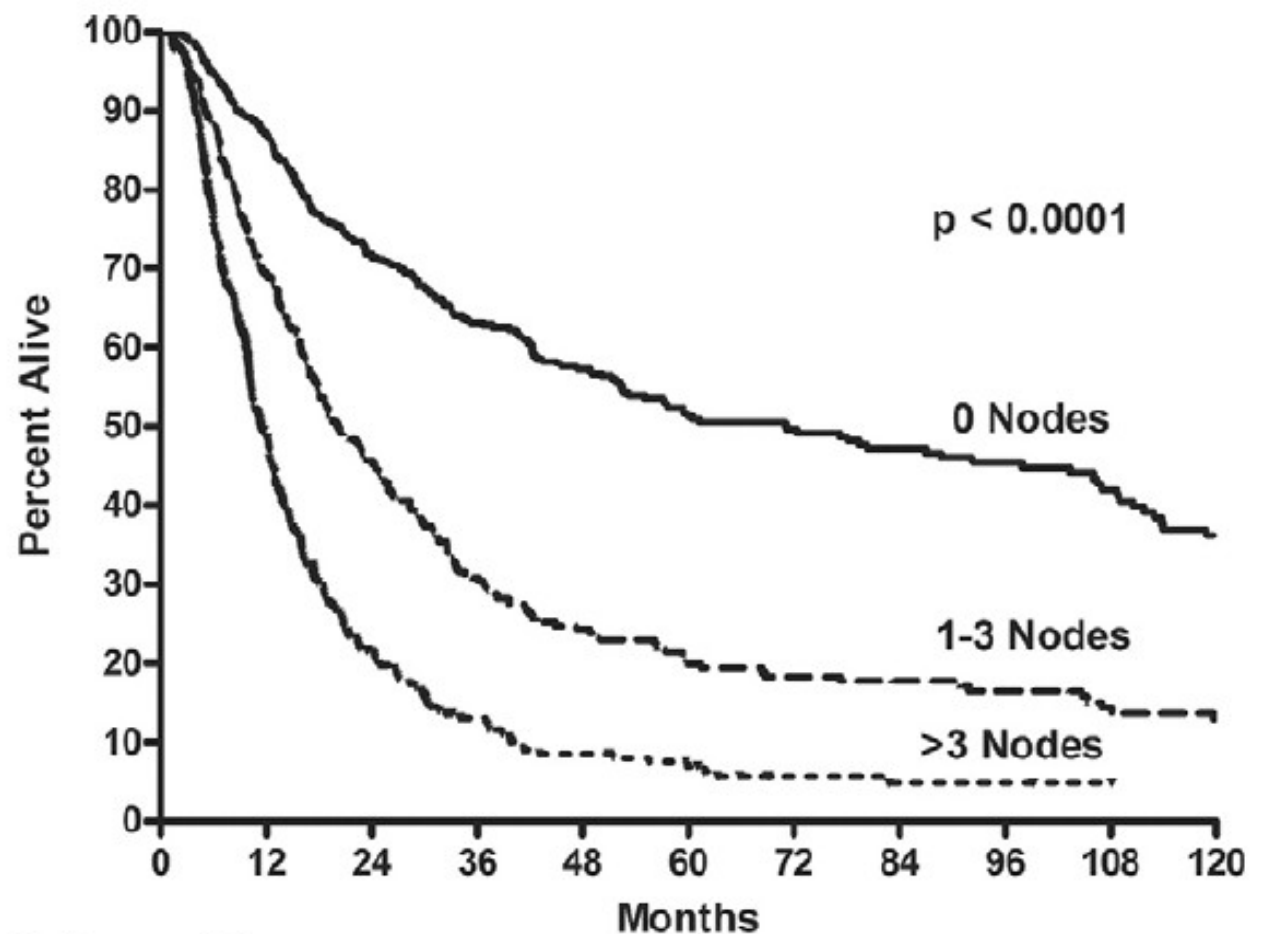
N0	496	223	136	71	45
N1	441	85	38	26	17
M1a	73	16	12	6	5
M1b	17	0	0	0	0

Fig 2. Kaplan-Meier survival, patients grouped by current American Joint Commission on Cancer (AJCC) nodal staging.

Kaplan-Meier Survival – By Current AJCC Staging

- Kaplan-Meier survival curves were distinct for nodal stages N0 and M1b, the N1 and M1a survival curves cross and are virtually interchangeable.
- When the data are analyzed in subgroups according to patients who received surgery only or induction therapy, the graphs are nearly identical to that of the whole cohort, and the overlap between the N1 and M1a groups persists

Kaplan-Meier Survival - By Num. of Involved LNs



Patients at risk:

0	496	223	140	71	45
1-3	299	75	38	26	18
>3	232	2	12	6	4

Fig 3. Kaplan-Meier survival, patients grouped by number of involved lymph nodes.

Kaplan-Meier Survival - By Num. of Involved LNs

- Based on previous publications
- The number of lymph nodes involved was strongly associated with long-term survival ($p < 0.001$)
- Kaplan-Meier survival curves show ordered, distinct curves when analyzing survival by number of nodes involved
- Three-year survival for 0, 1 to 3, and more than 3 lymph nodes was 63%, 31%, and 13%, respectively

Univariate Analysis

Table 2. Univariate Analysis and Survival of Resected Patients According to Nodal Disease

Risk Factor	N	HR (CI)	MS (mos)	3-Year Survival	5-Year Survival	<i>p</i> Value
Current pTNM						
N0	496	1.00 (ref)	72.4	63%	52%	< 0.001
N1	441	2.72 (2.30, 3.21)	16.7	24%	14%	
M1a	73	2.71 (2.04, 3.59)	13.9	23%	19%	
M1b ^a	17	6.94 (4.22, 11.41)	9.2	0%	0%	
Number of nodes involved						
0	496	1.00 (ref)	72.4	63%	52%	< 0.001
1–3	299	2.17 (1.81, 2.61)	20.4	31%	20%	
>3	232	4.12 (3.40, 4.98)	11.4	13%	7%	

Statistical Analysis

- Univariate analysis shows that nonregional lymph node metastasis was associated with a significantly decreased overall survival compared with regional or celiac nodal involvement ($p < 0.001$)
- The hazard ratios and confidence intervals of the N1 and M1a groups overlap completely
- Multivariable Cox proportional-hazards analysis including T, M, and num. of involved LNs shows all three are independent predictive factors of long-term survival ($p < 0.001$)

Modified Nodal-Status

- Based on the above findings, modifications to the current AJCC nodal staging system were derived:
 - **pN0:** no nodal metastasis
 - **pN1:** 1 - 3 regional lymph node metastasis, inclusive of previously designated M1a nodes
 - **pN2:** more than 3 regional lymph node metastasis, inclusive of M1a nodes
 - **pN3:** nonregional nodal involvement (previously M1b)

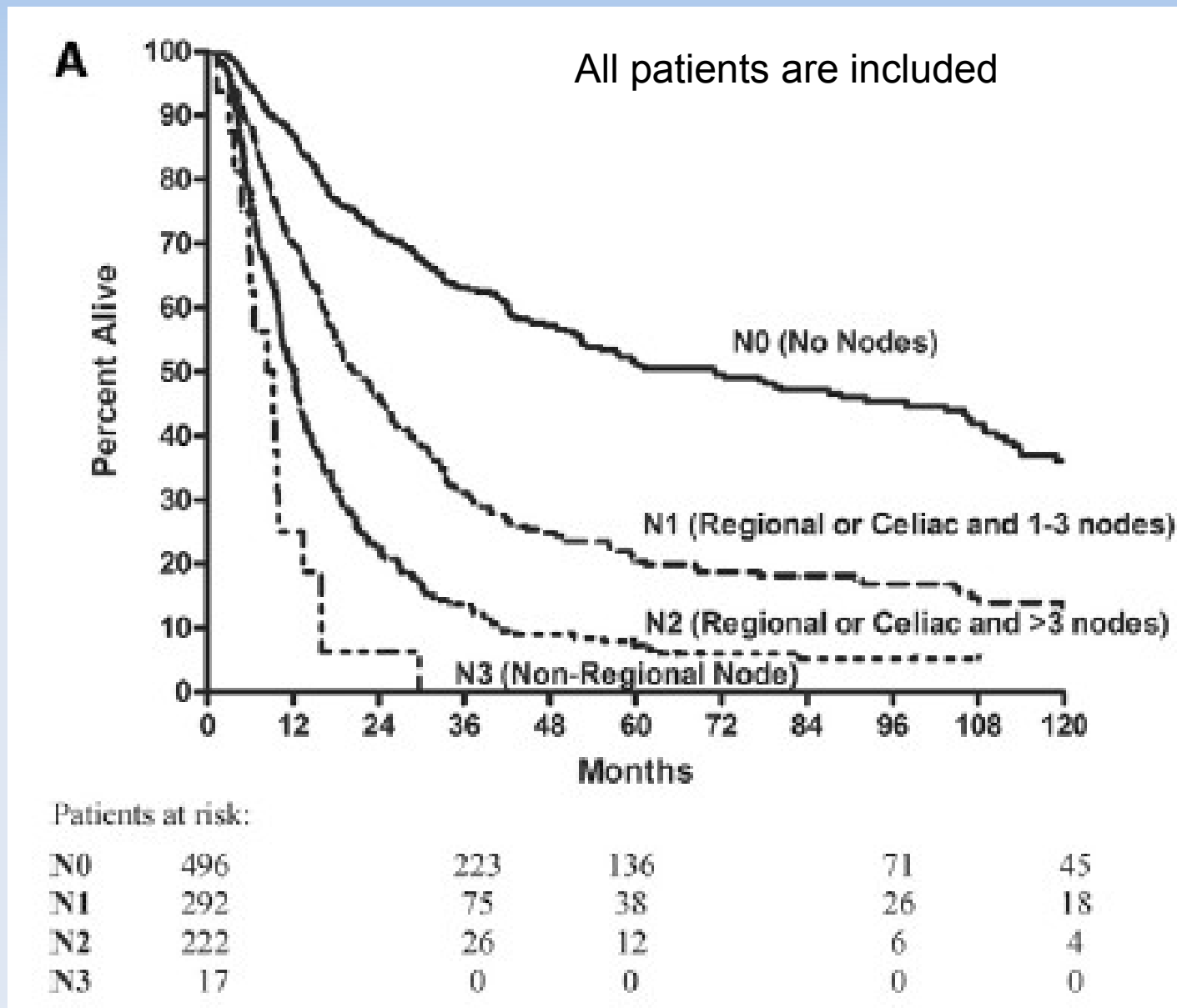
Univariate Analysis

Table 2. Univariate Analysis and Survival of Resected Patients According to Nodal Disease

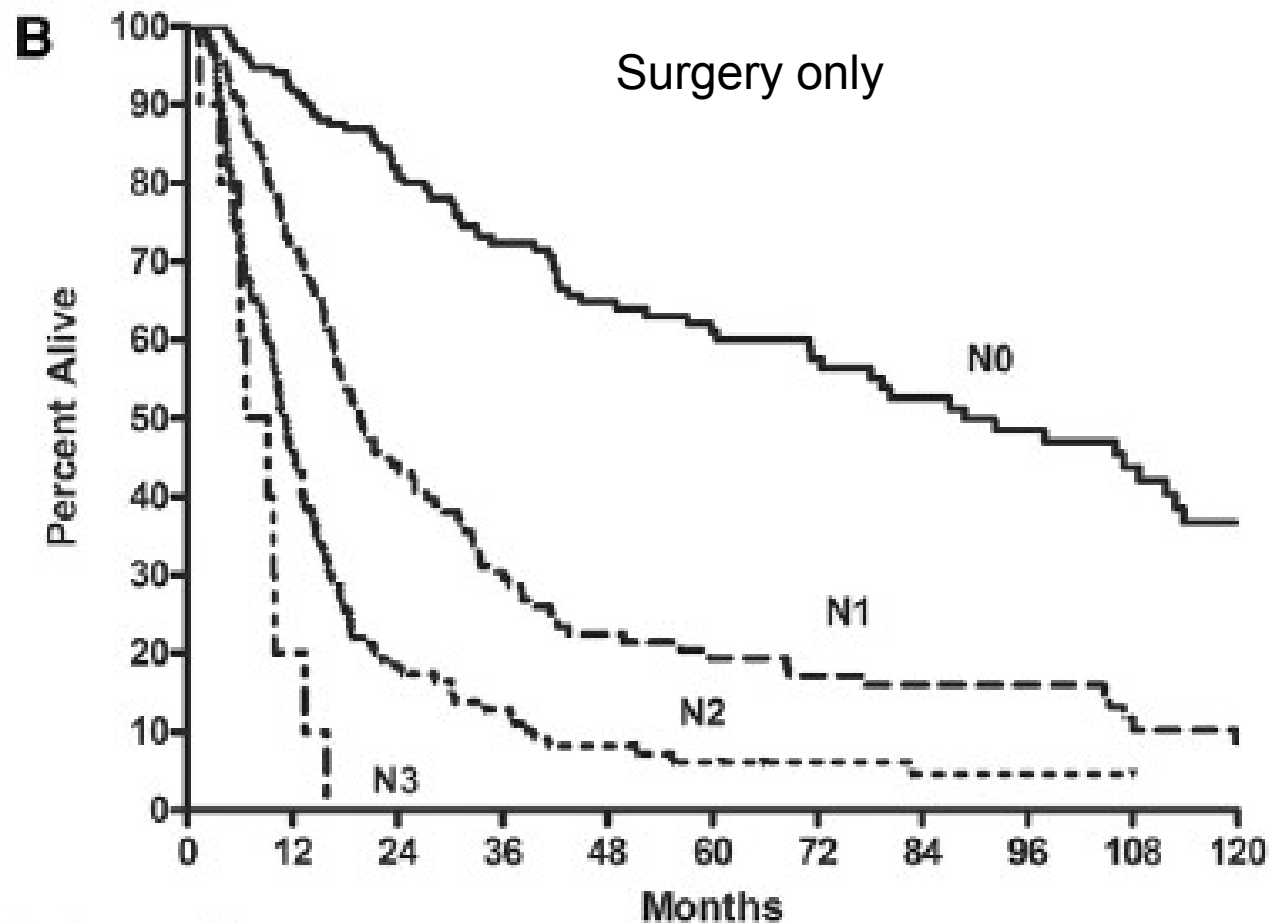
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1–3	299	2.17 (1.81, 2.61)	20.4	31%	20%	
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Modified N staging						
N0	496	1.00 (ref)	72.4	63%	52%	< 0.001
N1	292	2.14 (1.78, 2.57)	20.4	32%	20%	
N2	222	4.01 (3.31, 4.87)	12	14%	7%	
N3	17	7.16 (4.35, 11.78)	9.1	0%	0%	
Modified N staging, surgery only						
N0	174	1.00 (ref)	92.3	73%	61%	< 0.001
N1	131	2.85 (2.13, 3.83)	19.6	30%	19%	
N2	116	5.67 (4.20, 7.66)	11.1	13%	6%	
N3	11	10.26 (5.38, 19.58)	9.1	0%	0%	
Modified N staging, induction therapy + surgery						
N0	322	1.00 (ref)	52.6	58%	46%	< 0.001
N1	161	1.82 (1.43, 2.32)	23	33%	21%	
N2	106	3.18 (2.45, 4.13)	12.5	15%	8%	
N3	6	5.37 (2.37, 12.20)	8.4	0%	0%	

^a M1b by nonregional nodal disease only.

Survival Curve by the Proposed Staging System



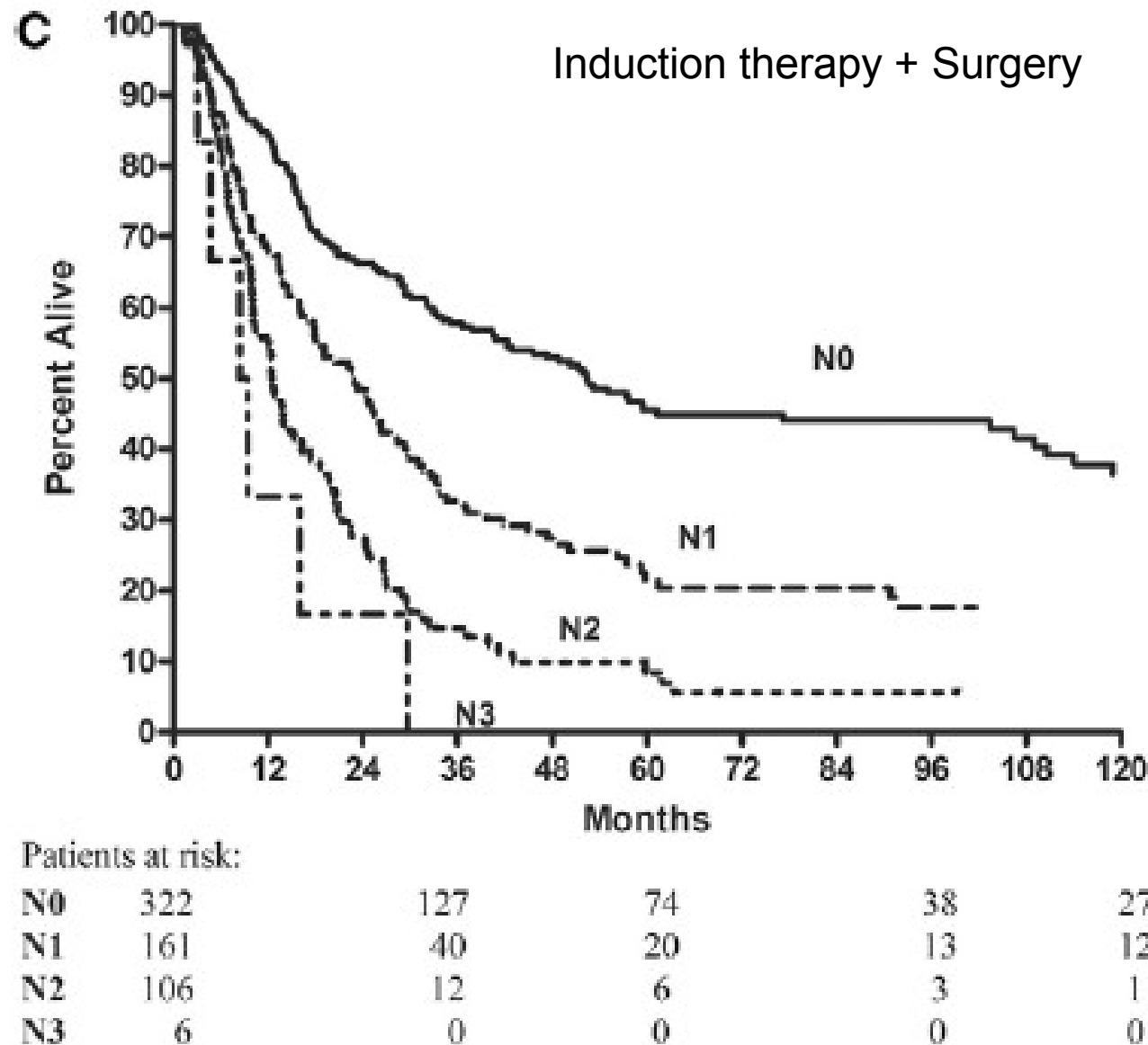
Survival Curve by the Proposed Staging System



Patients at risk:

N0	174	96	62	33	18
N1	131	35	18	13	6
N2	116	14	6	3	2
N3	11	0	0	0	0

Survival Curve by the Proposed Staging System



Discussion – Superiority of the Proposed System

- Eliminates the cumbersome M1a classification while including all lymph node disease within the N category, reserving the M category for visceral metastatic disease
- Incorporates patients treated with induction therapy and effectively predicts survival in that subgroup of patients
- The modified system is a statistically significant improvement over the current system

Discussion – Problems

- The impact of pathologic downstaging from this preoperative treatment on the pTNM staging system has not been fully evaluated
- Not account for other tumor features such as length, micrometastasis, molecular markers, or various histologic features
- Whether three involved nodes is the correct inflection point is not known
- Data set is too small to refine the entire staging system

Conclusion

- Modification of the AJCC nodal classification system to incorporate the number of involved lymph nodes with regional and nonregional node location simplifies and better predicts long-term survival than does the current AJCC nodal system.