A propensity-matched analysis comparing survival after primary minimally invasive esophagectomy followed by adjuvant therapy to neoadjuvant therapy for esophagogastric adenocarcinoma

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ABSTRACT

Objectives: Prognosis for patients with locally advanced esophagogastric adenocarcinoma (EAC) is poor with surgery alone, and adjuvant therapy after open esophagectomy is frequently not tolerated. After minimally invasive esophagectomy (MIE); however, earlier return to normal function may render patients better able to receive adjuvant therapy. We examined whether primary MIE followed by adjuvant chemotherapy influenced survival compared with propensity-matched patients treated with neoadjuvant therapy.

Methods: Patients with stage II or higher EAC treated with MIE (N = 375) were identified. Using 30 pretreatment covariates, propensity for assignment to either neoadjuvant followed by MIE (n = 183; 54%) or MIE as primary therapy (n = 156; 46%) was calculated, generating 97 closely matched pairs. Hazard ratios were adjusted for age, sex, body mass index, smoking, comorbidity, and final pathologic stage.

Results: In propensity-matched pairs, adjusted hazard ratio for death did not differ significantly for primary MIE compared with neoadjuvant (hazard ratio, 0.83; 95% confidence interval, 0.60-1.16). Recurrence patterns were similar between groups and 65% of patients with IIb or greater pathologic stage received adjuvant therapy. Clinical staging was inaccurate in 37 out of 105 patients (35%) who underwent primary MIE (n = 18 upstaged and n = 19 downstaged).

Conclusions: Primary MIE followed by adjuvant chemotherapy guided by pathologic findings did not negatively influence survival and allowed for accurate staging compared with clinical staging. Our data suggest that primary MIE in patients with resectable EAC may be a reasonable approach, improving stage-based prognostication and potentially minimizing overtreatment in patients with early stage disease through accurate stage assignments. A randomized controlled trial testing this hypothesis is needed. (*J Thorac Cardiovasc Surg* 2015;149:538-47)

Survival of propensity-matched groups.

Central Message

Primary minimally invasive esophagectomy produced more accurate staging and did not negatively impact survival compared with clinical staging.

Clinical Relevance

Primary minimally invasive esophagectomy followed by adjuvant therapy in patients with locally advanced esophagogastric adenocarcinoma may be a reasonable alternative to treating all with neoadjuvant therapy. This approach permits accurate stage assignment and could improve prognostication and minimize the risk of overtreatment in patients with early-stage disease.

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Supported by award Nos. K07CA151613 (to K.S.N.), UL1 RR024153, and UL1TR000005 from the National Cancer Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Disclosures: James D. Luketich reports equity ownership in Intuitive Surgical. Omar Awais reports consulting fees from Baxter and lecture fees from Covidien. All other authors have nothing to disclose with regard to commercial support.

Read at the Residents & Fellows Research Conference and Plenary Session of the 53rd Annual Meeting of the Society for Surgery of the Alimentary Tract, San Diego, California, May 18 and 21, 2012.

Received for publication Feb 14, 2014; revisions received Sept 22, 2014; accepted for publication Oct 6, 2014; available ahead of print Nov 24, 2014.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2014.10.044>

The rationale for trimodality therapy in the management of esophagogastric adenocarcinoma (EAC) is treatment of systemic micrometastasis and tumor downstaging, thus increasing the likelihood of complete resection, local control, and overall survival.¹⁻⁴ Patients who maintain a reasonable performance status after neoadjuvant chemo(radio)therapy undergo esophagectomy with regional lymphadenectomy. In theory, this rationale is sound. In practice, great variability in neoadjuvant regimens exists between centers,⁵ and when studied in randomized controlled trials, comparisons between multimodal therapy and surgery alone yield conflicting results.⁶⁻¹¹ Lack of consistent neoadjuvant regimens is compounded by the limitations of clinical staging,¹²⁻¹⁷ and differences in approach to esophagectomy, extent of lymphadenectomy, and perioperative outcomes

Abbreviations and Acronyms

AJCC	= American Joint Committee on Cancer
CCI	= Charlson Comorbidity Index
CT	= computed tomography
EAC	= esophagogastric adenocarcinoma
EUS	= endoscopic ultrasound
MIE	= minimally invasive esophagectomy
PET	= positron emission tomography

between centers.^{18,19} Finally, lack of proven adjuvant therapies and difficulties administering chemotherapy after open esophagectomy have led some investigators to conclude that neoadjuvant therapy is the only option.^{20,21}

In our center, we perform minimally invasive esophagectomy (MIE), regardless of tumor stage or the use of neoadjuvant therapy. We hypothesized that patients treated with primary MIE followed by adjuvant therapy would have comparable oncologic outcomes compared with patients treated with neoadjuvant therapy followed by MIE. Because treatment assignment was not random, we adjusted for large differences in observed covariates between groups using a propensity score and examined whether primary MIE followed by adjuvant chemotherapy influenced survival compared with propensity-matched patients treated with neoadjuvant therapy.

PATIENTS AND METHODS

We reviewed all patients with clinical stage II or higher EAC treated with MIE (January 1, 1997-July 31, 2009; N = 375). Our approach to MIE has been previously described.²²⁻²⁵ Eight stage IVb patients who underwent MIE for bleeding and/or perforation and were excluded. Pretreatment nodal and distant metastases were evaluated with computed tomography (CT) scan (n = 339), positron-emission testing (PET) scan (n = 110), endoscopic ultrasound (EUS) (n = 244), and/or laparoscopic staging (n = 150). Because the number of clinically positive nodes were not routinely reported, clinical stage was assigned using the American Joint Committee on Cancer (AJCC) sixth edition.²⁶ Definitive pretreatment clinical stage was assigned only if tumor depth was assessed by EUS; when EUS was not performed or available for review, overall pretreatment clinical stage was considered undocumented unless CT or PET revealed celiac node involvement, which is stage IVa disease, according to the AJCC.

Propensity-Score Matching

We generated propensity scores to determine the probability of treatment assignment to either group. The dependent variable in the logistic regression model was treatment assignment (neoadjuvant [E-] or primary MIE [E+]); the independent variables were clinically relevant pretreatment covariates (Table 1). Patients were then matched without replacement and without ties. Due to perfect separation between neoadjuvant and primary MIE, patients with nonelective surgery (n = 11), other metastatic tumor (n = 2), cervical mass location (n = 1), or clinical tumor stage T1 (n = 8) were excluded from propensity scoring. Six patients were excluded because of missing data in 1 or more propensity scoring variables. Propensity scores were generated for 339 patients representing the final unmatched cohort (Table 2).

We took each exposure patient ([E+] primary MIE), 1 at a time, and found all control patients ([E-] neoadjuvant therapy followed by MIE) still in the matching pool whose propensity scores were within 0.05 of the exposure patient's score. If a suitable match was not available, the patient was not included in the matched dataset. Matching was repeated several times with different random number generator seeds to ensure that matching balance and final outcome analysis produced similar, stable results each time, regardless of random seed. (Data not shown.)

Before propensity-score matching, neoadjuvant patients were significantly younger and more likely to have daily alcohol use and pretreatment complaints of dysphagia, whereas patients with primary MIE had higher age-adjusted Charlson Comorbidity Index (CCI) scores ($P = .025$).²⁷ At least 1 comorbid condition was present in 56% of patients (range, 1-6; n = 190 out of 339) and 2 or more comorbid conditions were present in 22% (n = 74 out of 339). EUS showing pretreatment invasion into the muscularis propria (T2) was more common in the patients with primary MIE; they were also less likely to have adventitial (T3) invasion. Pretreatment clinical stage III to IVa was more common in the neoadjuvant cohort, but there were no differences in pretreatment nodal metastasis rates, tumor location, or grade (Table 2).

Ninety-seven closely matched pairs (n = 194) were generated using Stata.²⁸ Before matching, overall mean percent bias was 15.2% ($P < .001$ for differences between the cohorts). After matching, overall mean percent bias was 6% ($P = .973$), with <10% bias for most variables and <20% in all variables except history of smoking (Table 3). Age (median, 64 years for both; $P = .895$) and age-adjusted CCI score (2 vs 1.5; $P = .2757$) were similar between matched and unmatched patients; median survival was 20.3 versus 23.65 months ($P = .1094$) and recurrence rates were 58% versus 53% ($P = .377$), respectively. The area under the receiver operator characteristic (ROC) curve (c-index) was 0.778, indicating very good discrimination.

Statistical Analysis

Statistical analysis was performed using Stata 13, summarizing descriptive statistics with frequencies and percentages for categorical variables and median with interquartile range (IQR) for continuous variables. Variables associated with adjuvant therapy were assessed using logistic regression. Data missingness was random. Survival time was defined as time from esophagectomy to date of last living contact or death. Time to recurrence was defined as time from esophagectomy to last clinical evaluation for recurrence. Survival curves for matched cohorts were compared using log-rank test for equality of survivor functions. Hazard ratios for death were calculated using stratified (matched) Cox proportional hazards regression with clustered standard errors for pairs after controlling for age, sex, body mass index, smoking, age-adjusted CCI, and final AJCC 7 pathologic stage.²⁹

RESULTS

Treatment and Perioperative Outcomes for the Entire Cohort

Initial therapy was MIE in 156 patients (46%) and neoadjuvant therapy in 183 patients (54%; 51% chemotherapy alone and 49% chemoradiation). Over the 12-year time-frame, neoadjuvant therapy use ranged from 30% to 70% per year, but has been stable between 40% and 50% since 2006. Cisplatin (76%), 5-fluorouracil (61%), and paclitaxel (44%) were used in combination in 32% of patients; 19% received the combination of 5-fluorouracil and cisplatin. Carboplatin (19%), oxaliplatin (2%), irinotecan (23%), docetaxel (6%), and epirubicin (6%) were used in combination in the remaining patients. Median delivered radiation dose was 5040 cGray (IQR, 4500-5040 cGy).

TABLE 1. Variables used for propensity scoring

Age	Final pretreatment clinical stage	Surgeon*	Any neurologic disorder
Sex	Final pretreatment T stage	Urgency of operation	History of cerebrovascular accident
Smoking history	Final pretreatment N stage	Reoperation	History of transient ischemic attack
Body mass index	Final pretreatment M stage	History of myocardial infarction	Malignancy other than current
Daily alcohol use	History of Barrett's esophagus	Coronary artery bypass graft	Metastatic cancer
Gastroesophageal reflux disease	Location of mass in esophagus	History of CHF	Liver disease
Dysphagia	Pretreatment tumor grade	Renal insufficiency or failure	Vascular disease
		Diabetes mellitus	Pulmonary disease

CHF, Congestive heart failure. *James D. Luketich, MD.

A median of 21 lymph nodes were identified in the pathologic specimen after MIE, with slightly fewer lymph nodes examined in the neoadjuvant group. R0 resection, defined as complete resection of all gross and microscopic disease, and negative mucosal margins were achieved in 97% of patients ($n = 329$), with no difference between groups. Neoadjuvant therapy specimens were more likely to be node-negative, have lower pathologic grade, smaller tumor size, and less likely to have angiolymphatic invasion at resection, whereas primary MIE specimens were more likely to have tumor cells at the radial margin (Table 4).

Median survival for the overall cohort was 22.6 months (IQR, 9.9-47.8).

Pathologic Complete Response (PCR) and Prognosis

PCR (13.1%) differed significantly between patients treated with chemoradiation (25%; 22 out of 88 patients) and chemotherapy alone (2.1%; 2 out of 94 patients; $P < .001$). Median survival after neoadjuvant chemoradiation ($n = 88$), was 36.2 versus 18.2 months when PCR occurred (log-rank test $P = .02$). When survival in PCR patients was compared with the combined group of patients with residual tumor after neoadjuvant therapy and primary MIE, a survival advantage after neoadjuvant therapy was not realized, although there was a trend toward significance (median, 39.5 vs 21.9 months; log-rank test $P = .09$).

Administration of Adjuvant Therapy in the Overall Cohort

Data regarding adjuvant therapy was available for 311 patients overall (92%) and 178 matched patients (92%). Adjuvant chemotherapy was administered to 49% of neoadjuvant (86 out of 176) and 49% of primary MIE patients (66 out of 135; $P = 1.000$). Factors associated with adjuvant therapy included age at operation ($P < .001$) and age-adjusted CCI ($P < .001$). Pathologic tumor factors associated with adjuvant therapy in univariate analysis include AJCC 7 pathologic stage II or greater ($P < .001$),²⁹ T3 depth of invasion ($P = .002$), presence and increasing number of pathologically positive nodes ($P < .001$ for both), viable tumor at esophagectomy ($P = .001$), larger pathologic tumor size ($P < .001$), angiolymphatic invasion ($P = .047$), positive

circumferential ($P = .005$) and mucosal ($P = .01$) margins, pathologic grade ($P < .001$), and R0 resection ($P = .100$). After adjusting for all significant variables, age younger than 70 years ($P = .001$) and CCI score < 3 ($P = .014$) were the only significant predictors of exposure to adjuvant therapy. The c-statistic for the logistic model was 0.778, indicating good discrimination for predicting adjuvant therapy after MIE.

Propensity-Score Matched Recurrence and Survival Analysis

In the 97 propensity-score matched pairs, median time to last clinical follow-up or death was 20.3 months (IQR, 9.9-43.9). Median overall survival was 18.7 months (IQR, 9-36), with no difference between propensity-score matched groups (Figure 1, A) (log-rank test $P = .679$). To account for paired data and censoring, multivariate clustered Cox regression was performed. After adjusting for age, sex, body mass index, smoking, age-adjusted CCI score, and AJCC 7 pathologic stage,²⁹ primary MIE was not associated with significantly different hazard for death (hazard ratio, 0.83; 95% confidence interval, 0.60-1.16). Pathologic stage was a significant prognostic variable ($P = .006$).

In the 97 propensity-score matched pairs, 113 patients (58%) had developed recurrence at a median follow-up of 10.1 months (IQR, 4.1-21.1) with no difference between propensity score-matched groups in either the proportion with recurrence (neoadjuvant 55 out of 97 [57%] vs primary MIE 58 out of 97 [60%], respectively; $P = .771$) or time to recurrence (mean 14.9 vs 15.8 months, respectively; log-rank test $P = .924$) (Figure 1, B). When identified, recurrence was distant in 76% and 78% of neoadjuvant (42 out of 55) and primary MIE patients (45 out of 58; $P = .118$), respectively. Chemotherapy alone showed a trend toward higher recurrence rates compared with chemoradiation (64% [38 out of 59 patients] vs 45% [17 out of 38 patients]; $P = .063$), with 76% of patients (29 out of 38) and 77% of patients (13 out of 17) presenting with distant metastasis, respectively.

Administration of Adjuvant Therapy in the Propensity-Score Matched Cohort

In the propensity-score matched cohort, adjuvant therapy was given to 47% of the neoadjuvant cohort (43 of 92 with

TABLE 2. Pretreatment patient demographics and characteristics for the entire cohort comparing patients assigned to neoadjuvant therapy with those assigned to minimally invasive esophagectomy (MIE) as primary therapy

Pretreatment clinical characteristic	Before matching in propensity-scored patients			P value
	Primary MIE (n = 156)	Neoadjuvant therapy (n = 183)	All patients (n = 339)	
Age, y	67 (59-75)	63 (54-70)	64 (56-72)	<.001
Body mass index	27.4 (24.8-30.9)	27.2 (23.6-31.1)	27.3 (24.4-31)	.472
Male sex	131	157	288	.651
Surgeon*	99	138	237	.018
History of smoking (>100 cigarettes in lifetime)	111	144	255	.130
Daily alcohol use	17	36	53	.035
Pretreatment dysphagia	115	159	274	.002
Documented history of gastroesophageal reflux disease	107	115	222	.303
Histologically confirmed Barrett's esophagus	92	96	188	.273
Prior esophageal operation	12	8	20	.249
Comorbid illnesses				
Overall age-adjusted Charlson Comorbidity Index Score	3 (0-4)	1 (0-4)	2 (0-4)	.025
Myocardial infarction or revascularization	37	35	72	.351
Coronary bypass graft or stent	27	22	49	.215
Congestive heart failure	5	4	9	.738
Peripheral vascular disease	9	12	21	.824
Creatinine ≥ 2.0 or need for hemodialysis	1	2	3	1.000
Diabetes requiring medical therapy	29	23	52	.133
Pulmonary disease	30	38	68	.786
Neurological disorder	13	8	21	.175
Transient ischemic attack	10	5	15	.117
Cerebrovascular accident	5	4	9	.738
Malignancy other than esophageal cancer	10	13	23	.832
Liver dysfunction (child's class A, B, or C)	2	3	5	1.000
Pretreatment tumor-specific variables				
Pretreatment location of mass by endoscopy				1.000
Middle esophagus	1	1	2	
Lower esophagus	48	56	104	
GEJ/cardia	107	126	233	
Pretreatment tumor grade				.113
Well differentiated	15	6	21	
Moderately differentiated	43	58	101	
Poorly differentiated	75	91	166	
Not reported	23	28	51	
Final pretreatment tumor depth*				.002
T2 (into muscularis propria)	29	19	48	
T3 (into adventitia)	74	119	193	
T4a (into adjacent, resectable structures)	2	6	8	
Pretreatment T stage unknown	51	39	90	
Final pretreatment nodal status†				.919
N0 (no clinically positive nodes)	36	43	79	
N1 (clinically positive nodes)	117	135	252	
N stage unknown	3	5	8	
Final pretreatment clinical stage				<.001
Stage IIa	3	19	22	
Stage IIb	27	14	41	
Stage III	69	91	160	
Stage IVa (celiac node involvement)	6	26	32	
Pretreatment stage undocumented	51	33	84	

Values are presented as n or median (interquartile range). *MIE*, Minimally invasive esophagectomy; *GEJ*, gastroesophageal junction. *Pretreatment tumor depth assigned only for those patients with a pretreatment endoscopic ultrasound documenting depth of invasion into the esophageal wall. Pretreatment T stage was not assigned based on computed tomography signs or symptoms. †Pretreatment node status assigned based on computed tomography scan, positron emission tomography scan, endoscopic ultrasound, and/or laparoscopic staging.

TABLE 3. Comparison of clinical variables between groups after propensity score assignment and after propensity matching

Pretreatment clinical characteristics	Before matching in propensity-scored patients			Matched cohort			% Bias reduction
	Primary MIE	Neoadjuvant therapy	% Bias	Primary MIE	Neoadjuvant therapy	% Bias	
	(n = 156)	(n = 183)		(n = 97)	(n = 97)		
Mean age, y	66.4	61.7	44	64.1	63.5	5.8	86.9
Mean body mass index	28.6	28.1	7.8	29.4	29.3	1.9	75.6
Male sex	84	86	−5.1	82.5	82.5	0	100
Surgeon*	63.5	75.4	−26.2	74.2	66	18	31
History of smoking (>100 cigarettes in lifetime)	71.2	78.7	−17.4	81.4	71.1	23.8	−36.8
Daily alcohol use	10.9	19.7	−24.5	13.4	9.3	11.5	53
Pretreatment dysphagia	73.7	86.9	−33.5	85.6	84.5	2.6	92.2
Documented history of gastroesophageal reflux disease	68.6	62.8	12.1	65	68	−6.5	46.2
Histologically confirmed Barrett's esophagus	59	52.5	13.1	55.7	60.8	−10.4	20.9
Prior esophageal operation	7.7	4.4	13.9	4.1	4.1	0	100
Charlson-defined comorbid illness							
History of myocardial infarction or revascularization	23.7	19.1	11.2	19.6	20.6	−2.5	77.6
History of coronary bypass graft or stent	17.3	12	14.9	14.4	14.4	0	100
History of congestive heart failure	3.2	2.2	6.3	4.1	3.1	6.3	−1.1
History of peripheral vascular disease	5.8	6.6	−3.3	5.2	5.2	0	100
Creatinine ≥2.0 or need for hemodialysis	0.6	1.1	−4.9	1	1	0	100
Diabetes requiring medical therapy	18.6	12.6	16.6	16.5	17.5	−2.8	82.9
History of pulmonary disease	19.2	20.8	−3.8	20.6	19.6	2.6	32.8
History of neurological disorder	8.3	4.4	16.2	6.2	7.2	−4.2	74
History of transient ischemic attack	6.4	2.7	17.6	4.1	4.1	0	100
History of cerebrovascular accident	3.2	2.2	6.3	1	3.1	−12.7	−102.3
History of malignancy other than esophageal cancer	6.4	7.1	−2.8	7.2	5.2	8.2	−197.3
History of liver dysfunction (child's class A, B or C)	1.3	1.6	−3	2.1	1	8.6	−188.5
Pretreatment tumor-specific variables							
Pretreatment location of mass by endoscopy							
Middle esophagus	0.64	0.55	1.2	1	1	0	100
Lower esophagus	30.8	30.6	0.4	29.9	30.9	−2.2	−513.1
GEJ/cardia	68.6	68.9	−0.6	69.1	68	2.2	−292.4
Pretreatment tumor grade							
Well differentiated	9.6	3.3	25.9	7.2	5.2	8.4	67.5
Moderately differentiated	27.6	31.7	−9	28.9	33	−9	0.1
Poorly differentiated	48.1	49.7	−3.3	50.5	52.6	−4.1	−25
Not reported	14.7	15.3	−1.6	13.4	9.3	11.5	−640.4
Individual and overall pretreatment clinical stage variables							
Final pretreatment tumor depth†							
T2 (into muscularis propria)	18.6	10.4	23.4	12.4	15.5	−8.8	62.3
T3 (into adventitia)	47.4	65	−35.9	55.7	55.7	0	100
T4a (into adjacent, resectable structures)	1.3	3.3	−13.4	2.1	2.1	0	100
Pretreatment T stage unknown	32.7	21.3	25.8	29.9	26.8	7	72.8
Final pretreatment nodal status‡							
N0 (no clinically positive nodes)	23.1	23.5	−1	21.7	15.5	14.6	−1371.5
N1 (clinically positive nodes)	75	73.8	2.8	76.3	81.4	−11.8	−319.2
N stage unknown	1.9	2.7	−5.4	2.1	3.1	−6.8	−27.4

(Continued)

TABLE 3. Continued

Pretreatment clinical characteristics	Before matching in propensity-scored patients			Matched cohort			% Bias reduction
	Primary MIE (n = 156)	Neoadjuvant therapy (n = 183)	% Bias	Primary MIE (n = 97)	Neoadjuvant therapy (n = 97)	% Bias	
Final pretreatment clinical stage							
Stage IIa	1.9	10.4	−35.7	3.1	1	−9.4	75.6
Stage IIb	17.3	7.7	29.4	10.3	13.4	−9.4	68
Stage III	44.2	49.7	−11	50.5	53.6	−6.2	43.7
Stage IVa (celiac node involvement)	3.9	14.2	−36.7	6.2	5.2	3.6	90.1
Pretreatment stage undocumented	32.7	18	34.1	29.9	26.8	7.2	78.9

Values are given as %, unless otherwise noted. MIE, Minimally invasive esophagectomy; GEJ, gastroesophageal junction. *James D. Luketich, MD. †Pretreatment tumor depth assigned only for those patients with a pretreatment endoscopic ultrasound documenting depth of invasion into the esophageal wall. Pretreatment T stage was not assigned based on computed tomography signs or symptoms. ‡Pretreatment nodal status assigned based on computed tomography scan, positron emission tomography scan, endoscopic ultrasound, and/or laparoscopic staging.

available data) compared with 56% of primary MIE patients (48 of 86 with available data; $P = .235$). Since 2006, adjuvant therapy was given to 65% of patients (41 out of 63 patients) in the matched pairs with pathologic stage IIb or greater, including 70% (33 out of 47) of primary MIE and 50% (8 out of 16) of neoadjuvant patients ($P = .224$).

Accuracy of Clinical Staging

Clinical staging was inaccurate in 35% of primary MIE patients who had complete clinical staging (EUS plus CT and/or PET-CT) before surgery (37 out of 105 patients). Eighteen patients were upstaged; 3 patients assigned to clinical stage IIa were stage IIIb ($n = 1$) and IIIc ($n = 2$) on final pathology. Thirteen patients assigned to clinical stage IIb were IIIa ($n = 7$), IIIb ($n = 3$), and IIIc ($n = 3$) on final pathology. Two patients with clinical stage III had resectable solitary liver metastasis discovered at esophagectomy and were assigned pathologic stage IV. Nineteen were downstaged after resection; 4 patients assigned clinical stage IIb were changed to stage IIa ($n = 3$) and Ib ($n = 1$) on final pathology. Fourteen patients assigned clinical stage III were reassigned to Ib ($n = 1$), IIa ($n = 4$), and IIb ($n = 9$) on final pathology. One patient assigned to clinical stage IVa was downstaged to stage IIb.

DISCUSSION

We performed a propensity-score matched analysis comparing neoadjuvant therapy followed by MIE to MIE as primary treatment for locally advanced EAC. We found that patients treated with primary MIE followed by adjuvant therapy based on pathologic stage did not differ significantly in terms of overall survival or recurrent disease compared with patients treated with neoadjuvant therapy. In addition, primary MIE allowed for accurate staging compared with clinical staging in nearly one-third of patients. These findings suggest that primary MIE followed by adjuvant therapy in patients with resectable locally advanced EAC is a reasonable alternative to treating all

patients with neoadjuvant therapy. By allowing accurate stage assignment through pathologic assessment of the primary tumor and the lymph nodes, MIE followed by adjuvant chemotherapy in appropriate patients could improve prognostication and potentially minimize the risk of over-treatment in patients with early stage disease.

Examining the Role of Neoadjuvant Therapy

There is little debate about the role of surgery in the management of EAC³⁰; analyses of large population-based datasets and single-center reports clearly demonstrate improved survival in patients treated with a trimodality approach compared with chemoradiation alone.^{31,32} The role for neoadjuvant therapy for EAC continues to be refined, in part because most of the randomized controlled trials comparing neoadjuvant therapy with surgery alone include both squamous and adenocarcinoma histologies. A recent meta-analysis suggested that patients with adenocarcinoma experience a survival benefit with neoadjuvant chemo(radio)therapy compared with surgery alone,^{2,11} as did the Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) trial,³³ which included adenocarcinoma histologic subtype for 75% of patients. In this study, the median survival for adenocarcinoma was approximately 28 months with surgery alone compared with 48 months after chemoradiotherapy followed by surgery ($P = .049$). However, when adjusted for baseline covariates, including sex, clinical N stage, and performance status, the 25.9% reduction in hazard for death in patients with adenocarcinoma treated with neoadjuvant chemoradiotherapy compared with surgery alone was not statistically significant.³³ In comparison, there was a nearly 58% reduction in hazard of death with chemoradiotherapy in the squamous histology group ($P = .007$). Although interpreted as a strong statement in favor of neoadjuvant chemoradiotherapy for all esophageal cancer patients, the survival benefit in the adenocarcinoma subset is less compelling, particularly when adjusted for other survival predictors. Importantly, as with other studies,

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TABLE 4. Pathologic outcomes after minimally invasive esophagectomy (MIE) comparing neoadjuvant therapy followed by MIE compared with MIE as primary treatment in propensity-matched and overall patient cohorts

Pathologic finding	Propensity-matched cohort			Overall cohort			
	Neoadjuvant therapy	Primary MIE	<i>P</i> value	Neoadjuvant therapy	Primary MIE	Total patients	<i>P</i> value
	(n = 97)	(n = 97)		(n = 183)	(n = 156)	(n = 339)	
Number of lymph nodes examined	20 (15-27)	25 (17-33)	.034	20 (14-27)	24 (16-32)	21 (15-29)	.003
Number of positive lymph nodes	1 (0-5)	3 (1-9)	.002	1 (0-4)	3 (1-7)	2 (0-6)	.002
Node-negative at resection	46 (47)	20 (21)	.001	79 (43)	36 (23)	122 (34)	.001
Pathologic grade			<.001				<.001
Well differentiated	1 (1)	1 (1)		1 (0.55)	4 (2)	4 (1.2)	
Moderately differentiated	35 (36)	35 (36)		66 (36)	53 (34)	119 (35)	
Poorly differentiated	40 (41)	61 (63)		78 (43)	99 (64)	177 (52)	
No residual tumor	15 (16)	0 (0)		30 (16)	0 (0)	30 (9)	
Unable to determine*	6 (6)	0 (0)		8 (4)	1 (0.6)	9 (3)	
Tumor size, cm	3.1 (0.5-5.3)	5 (3.5-6.5)	<.001	3.5 (0.3-5.2)	5 (3.5-6.5)	4 (2.3-6)	<.001
Angiolymphatic invasion†	40/81 (49)	76/93 (82)	<.001	80 (52)	115 (76)	195 (64)	<.001
Mucosal margins negative for tumor involvement	96 (99)	91 (94)	.118	180 (98)	149 (96)	329 (97)	.196
Tumor involving radial margin	7 (7)	13 (13)	.237	13 (7)	22 (14)	35 (10)	.048
R0 resection‡	96 (99)	91 (94)	.118	180 (98)	149 (96)	329 (97)	.196
American Joint Committee on Cancer 7 pathologic stage			<.001				<.001
Stage 0: Complete pathologic response§	15 (15.5)	NA		24 (13)	NA	24 (7.1)	
Stage IA	9 (9)	0 (0)		10 (5.5)	0 (0)	10 (3)	
Stage IB	5 (5)	4 (4)		12 (6.6)	8 (5)	20 (6)	
Stage IIA	4 (4)	5 (5)		7 (4)	9 (6)	16 (5)	
Stage IIB	15 (16)	15 (16)		37 (20)	30 (19)	67 (20)	
Stage IIIA	18 (19)	18 (19)		39 (21)	34 (22)	73 (22)	
Stage IIIB	11 (11)	20 (21)		21 (12)	31 (20)	52 (15)	
Stage IIIC	19 (20)	33 (34)		30 (16)	42 (27)	72 (21)	
Stage IV	1 (1)	2 (2)		3 (2)	2 (1)	5 (1.5)	

Values are presented as median (interquartile range) or n (%). NA, Not applicable; MIE, minimally invasive esophagectomy. *Tumor grade unable to be determined in patients with no residual tumor or only scattered residual cells. †Angiolymphatic invasion was not reported in the final pathology on all patients. ‡R0 resection is defined as a microscopically margin-negative resection, in which no gross or microscopic tumor remains in the primary tumor bed; R1 resection is defined as removal of all macroscopic disease but microscopic resection margins are positive. Radial margin involvement with tumor is not considered an R1 resection unless the tumor was adherent to adjacent structures (eg, liver, diaphragm, pleura, pericardium, or prevertebral fascia) and dissected free. R2 indicates gross residual tumor (primary tumor, regional nodes, and macroscopic margins) but does not indicate metastatic disease to distant organs. §Indicates no residual cancer within the esophagus or metastatic disease in the examined lymph nodes.

adjuvant therapy was not given to the surgery alone groups, meaning that patients with metastatic disease to the lymph nodes did not receive any systemic therapy. In contrast, adjuvant therapy was given to 65% of our propensity-score matched patients with IIB or greater pathologic stage and may explain the similar survival between groups in our study.

A major goal of neoadjuvant therapy is to achieve a complete pathologic response, with no residual disease in the esophagus or in the surrounding lymph nodes. However, in most studies, pathologic complete response is only found in 15% to 25% of patients treated with chemoradiation.³³⁻³⁷ The most recent randomized trial (the CROSS trial) had a 23% complete response rate after chemoradiotherapy in the adenocarcinoma group.³³ In patients treated with neoadjuvant chemotherapy without radiation, response rates range from 0% to 5%.^{10,38,39} The complete response rate in this study is consistent with the reported literature. When we examined the patients treated with chemoradiation, we did

see a significant improvement in survival associated with a PCR compared with chemoradiation patients without a complete response. This is also consistent with the reported literature.⁴⁰ We did not find improved survival with PCR compared with all patients with residual tumor at esophagectomy (including patients who did not have PCR after neoadjuvant and patients treated with primary MIE). Although potentially explained by insufficient power related to small numbers of PCR, the lack of survival advantage might be due to the delivery of adjuvant therapy to a high percentage of patients with nodal involvement after MIE as primary therapy. This possibility requires prospective validation in a randomized controlled trial.

In addition to optimizing survival, objective assessment of risks and benefits must be considered when analyzing the role for neoadjuvant therapy. Schneider and colleagues⁴¹ evaluated response to therapy and survival and found that patients in whom disease was stable (ie,

FIGURE 1. A, Overall survival after minimally invasive esophagectomy (MIE). Propensity-matched comparison of neoadjuvant therapy followed MIE compared with MIE as primary therapy. The numbers in parenthesis are the number of failure events (deaths) between each time point. B, Propensity-matched comparison of the percentage of patients free of recurrence over time after MIE. Neoadjuvant therapy followed by MIE versus MIE as primary therapy. The numbers in parentheses are the number of failure events (deaths) between each time point. In the primary MIE cohort, 1 patient had an R2 resection and persistent disease and was, therefore, never rendered free of disease. Number at risk, therefore, is 96 at time 0.

nonresponders) or who presented evidence for progression of disease had substantially worse survival than patients with a partial or complete response. In their study,⁴¹ objective tumor regression was noted at esophagectomy in only ~40% of patients; this means that 60% of patients derived no measurable benefit from the neoadjuvant therapy while being exposed to potential complications from the treatment itself. These complications were described in a systematic review of 38 articles by Courrech Staal and colleagues⁵; multiple grade III to IV toxicities associated with chemoradiation included dehydration (17%), vomiting (0%-16%), esophagitis (0%-43%), pneumonitis (2%), and fistula formation (2%). Treatment-related mortality was 2.3% (29 out of 1269 patients) after the start of chemoradiation therapy but before surgical resection.⁵ This variability in therapeutic response and risk of associated toxicity raises the possibility that a selective approach for patients treated outside of clinical trials may be worth further study. In some cases, patients with resectable disease at diagnosis may ultimately be unable to proceed with surgical resection because of treatment-related toxicity, or worsening of underlying comorbid conditions (such as pulmonary injury from the radiation field effect). In our study, patients who were older and who had a higher CCI score were less likely to have neoadjuvant therapy before MIE and were also less likely to have adjuvant therapy than were younger patients and those with fewer comorbidities. In fact, age younger than 70 years and CCI score < 3 were independently associated with the use of adjuvant therapy, whereas all of the tumor-specific variables (ie, the biological indicators of poor prognosis) were not. In many patients, because of toxicity risk, primary esophagectomy for resectable adenocarcinoma may be an important alternative, especially given that only 40% of patients benefit from current neoadjuvant regimens and one-third are incorrectly staged by clinical evaluation.

Study Strengths and Limitations

Several recent studies evaluating early outcomes after MIE versus open esophagectomy have shown significantly earlier return to baseline function, including global function, level of fatigue, overall physical function as measured by the physical component summary of the Short-Form 36 Health Survey (SF-36),⁴² quality of life measures such as pain and ability to talk, and activities of daily living. In a randomized controlled trial by Biere and colleagues,⁴³ these differences were identified as early as 6 weeks after esophagectomy. As with the randomized trial, Parameswaran and colleagues⁴⁴ noted faster resolution of physical fatigue, improving by 3 months and back to baseline at 6 months after MIE while remaining elevated after open esophagectomy. Reports of reduced motivation increased in the open group while the MIE group returned to baseline by 3 months and was below baseline (ie, more motivated) by 6 months. Finally, more MIE patients were completely independent in their instrumental activities of daily living at 3 and 6 months (53% vs 33% and 78% vs 33%, respectively). Although limited by small numbers of patients and there are no published studies to date that specifically examine the question of improved delivery of adjuvant therapy comparing open and MIE, these data suggest that the physiologic influence of MIE is of shorter duration and resolves within a timeframe (3 months) that would allow for adjuvant therapy to be considered. As noted in our study, 65% of our propensity-score matched patients with pathologic AJCC 7 stage IIB or greater (T3 depth of invasion and/or nodal metastasis in the pathologic specimen) received adjuvant therapy. The ability to deliver chemotherapy to patients with pathologically staged regionally advanced disease was likely an important factor in our finding that survival was similar between the propensity-score matched patients.

Our study is also strengthened by the use of propensity-score matching to equalize the treatment groups with regard

to variables such as age and clinical stage, which also affect survival. The propensity score is the conditional probability of an individual to be treated given its covariates⁴⁵; it is used to balance large differences in the observed covariates between 2 groups in observational studies, thereby reducing the bias in estimates of treatment effects. This allows investigators to adjust the likelihood of assignment to 1 treatment group versus another for as many covariates as possible. Using propensity-score matching, we created 2 treatment groups that were well balanced across nearly all levels of all included covariates.

Even with propensity matching, our comparisons between groups are limited by the completeness of the data and may be biased by difficult-to-measure factors, such as the thoroughness of documentation. We minimized this by performing chart review with consistent data definitions, and validation of the data by a second abstractor, but cannot completely correct for this limitation in retrospective study design. Another limitation of our study is that we are unable to discuss disease-specific mortality because the cause of death is unknown in patients who were followed-up by physicians close to their homes. As such, we compared overall survival only. Finally, the total number of patients in our study may not provide enough power to detect small but statistically significant differences in survival outcomes between groups.

Our results may not be generalizable to all surgeons and surgeon practices, particularly if they have limited experience with esophagectomy or operate in hospitals lacking the expertise to care for these patients postoperatively. In addition, the fact that our study population only includes patients who underwent MIE did not allow us to examine those patients who experienced disease progression, severe complications, and/or death while receiving neoadjuvant therapy, or who were treated with definitive chemo- and/or chemoradiotherapy.

CONCLUSIONS

We found that primary MIE followed by adjuvant chemotherapy does not negatively influence survival compared with propensity-matched patients treated with neoadjuvant therapy for locally advanced EAC, and allowed for accurate cancer staging. Our data suggest that similar outcomes can be achieved when patients undergo MIE with curative intent, followed by adjuvant chemotherapy for disease labeled pathologic stage IIB or greater. Patients with marginally resectable disease or significant nodal involvement should still be considered for neoadjuvant therapy to improve complete resection rates. We have previously shown that minimally invasive techniques for esophagectomy can be used in a wide range of patients; improved physiologic function in this setting may facilitate delivery of adjuvant chemotherapy.²⁵ This finding must be confirmed in prospective randomized trials before definitive conclusions can be made.

Future trials randomizing patients with EAC deemed resectable at laparoscopic staging to either neoadjuvant therapy followed by MIE or MIE followed by adjuvant therapy are needed to determine the true efficacy of this approach.

The authors thank Sunee Hempel, Megan Lunz, and Julie Ward for their assistance with data acquisition for this study. The authors also thank Shannon Wyszomierski for her excellent editorial review.

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Key words: neoadjuvant therapy, esophagectomy, propensity score, surgical procedures, minimally invasive, mortality