T2N0M0 esophageal cancer

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Objective: The study objective was to develop a treatment algorithm for cT2N0M0 esophageal cancer by determining (1) errors in clinical staging and (2) consequences of overtreatment and undertreatment of incorrectly clinically staged patients.

Methods: Of 742 clinically staged patients, 61 (8.2%) had cT2N0M0 cancer; 45 underwent surgery alone; 8 underwent surgery and postoperative adjuvant therapy; and 8 underwent induction therapy, then surgery. As reference, 31 of 666 patients (4.7%) who underwent surgery first had pT2N0M0 cancer and a 5-year survival of $61\% \pm 9.3\%$. Referent values were calculated from 445 clinically staged patients who underwent surgery first. Unmatched and matched survival comparisons were made using the log-rank test.

Results: Only 7 of 53 cT2N0M0 cancers treated with surgery first were pT2N0M0 (13% positive predictive value). Of incorrectly staged cT2N0M0 cancers (46/53), 29 (63%) were overstaged and 17 (37%) were understaged. Most overstaged cancers were pT1 (11 [38%] T1a and 15 [52%] T1b), and most understaged cancers were pN1 (13 [76%]). Matched overstaged patients treated by surgery alone (25/28) had a 5-year survival similar to that of patients with pTNM ($69\% \pm 9.8\%$ vs $63\% \pm 13\%$, $P = .8$). Understaged patients did better at 5 years than patients with pTNM if they had postoperative adjuvant therapy, not surgery alone ($43\% \pm 22\%$ vs $10\% \pm 9.5\%$, $P = .17$). Induction therapy decreased 5-year survival compared with all other treatment strategies ($13\% \pm 12\%$ vs $52\% \pm 7.4\%$, $P = .05$).

Conclusions: Patients with cT2N0M0 cancers should undergo surgery first with lymphadenectomy. Clinically understaged patients should receive postoperative adjuvant therapy. In the unlikely event that patients with cT2N0M0 cancers are found to have an uncommon pT2N0M0 cancer, they will have acceptable survival with surgery alone.

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Decision making in stage-directed therapy of esophageal cancer is easy at the extremes of stage grouping: surgery alone for early-stage cancers and multimodality therapy for advanced-stage cancers. Patients with pT2N0M0 esophageal cancer have intermediate survival with surgery alone (Figure 1). If decisions could be made on the basis of pathologic stage, surgery alone would be a logical choice for this cancer because adjuvant therapy is toxic and unlikely to measurably improve these patients' survival. However, decisions must be made on the clinical stage, and currently, this is guesswork for cT2N0M0 patients. The purpose of this study was to develop a logical algorithm for treating this cancer by determining (1) errors in its clinical staging and (2) consequences of overtreatment and undertreatment of incorrectly clinically staged patients.

Patients and Methods

Patients

A total of 742 patients with esophageal cancer who had clinical staging and esophagectomy from February 1987 through May 2005 were identified from the Cleveland Clinic Thoracic Surgery Database, which has been approved for use in research by the institutional review board. Three hundred forty patients underwent surgery alone, 105 patients underwent surgery

Abbreviations and Acronyms

EUS = endoscopic ultrasound

and postoperative adjuvant therapy, 121 patients underwent induction therapy and surgery, and 176 patients underwent induction therapy, surgery, and postoperative adjuvant therapy.

Clinical Staging

Clinical staging of T and N classifications was obtained by esophageal endoscopic ultrasound (EUS) performed under local sedation after flexible esophagoscopy. The currently available Olympus echoendoscope (Olympus Optical Co Ltd, Tokyo, Japan) (primarily EU-M2, EU-M3, and EU-M20) was used. Clinical classification of cT2 was invasion limited to the fourth ultrasound layer.^{1,2} Clinical classification of cN0 was no evidence of regional lymph node metastases. Classification was accomplished using established criteria for size, shape, border, and ultrasound “texture,” and was routinely assessed using the 7.5-MHz setting.²⁻⁴ Fifty-eight patients had EUS fine-needle aspiration of regional and nonregional lymph nodes. Clinical classification of cM0 was no evidence of distant metastases; all patients underwent computed tomography, and 273 patients underwent fluorodeoxyglucose positron emission tomography.

Errors in Clinical Staging

Referent values for EUS clinical classification of cT, cN, and cTNM were calculated from 445 clinically staged patients who underwent surgery first. The results are presented as sensitivity, specificity, positive and negative predictive values, and accuracy of EUS to identify T2, N0, and T2N0M0 cancers.⁵

Consequences of Treating Incorrectly Staged Patients

Overstaged patients. A total of 177 patients treated with surgery alone had <pT2N0M0 cancer. Among these, 28 patients were overstaged as cT2N0M0 and the remaining 149 patients were not. For fair survival comparisons, differences between these 2 groups of patients were accounted for with propensity methods.^{6,7} The probability of being a patient with overstaged cT2N0M0 cancer (propensity score) was estimated from a logistic regression model containing 5 variables: age, pT, histology, differentiation, and surgical approach. Patients were then matched using the propensity score. Twenty-five matched pairs were obtained.

Patient and tumor characteristics were compared between unmatched and matched groups using the *t* test or chi-square test. Survival after esophagectomy was estimated nonparametrically by the Kaplan–Meier method⁸ and compared between unmatched and matched groups using the log–rank test. Analyses were performed using SAS software (version 8, SAS Institute, Inc, Cary, NC).

Understaged patients. A total of 114 patients treated with surgery alone had >pT2N0M0 cancer; 10 patients were understaged as cT2N0M0, and 104 patients were not. One hundred patients treated with surgery followed by adjuvant therapy had >pT2N0M0 cancer; 7 patients were understaged as cT2N0M0, and 93 patients were not. Propensity models were developed separately for patients treated with surgery alone and patients

Figure 1. Survival after surgery alone for esophageal cancer according to pTNM. Each step represents a death, and vertical ticks represent a censored patient.

treated with surgery followed by adjuvant therapy. In each analysis, the probability of being an understaged cT2N0M0 patient was estimated from a logistic regression model containing 3 variables: pT, pN, and pM. Patients were then matched using the propensity score. Nine matched pairs were obtained for those treated with surgery alone, and 7 matched pairs were obtained for those treated with surgery followed by adjuvant therapy. Comparisons were made as previously described.

Presentation

Data are presented as frequencies and percentages or as means and standard deviations. Survival estimates are provided at selected time points, along with the standard error and number at risk.

TABLE 1. Referent values for clinical staging*

Pathologic finding	EUS determination		Referent values (%)				
	cT2	Not cT2	Acc	Sens	Spec	+PV	–PV
pT2	18	19	78	49	81	19	95
Not pT2	78	330					
	cN0	Not cN0					
pN0	185	89	71	68	78	83	60
pN1	38	133					
	cT2N0M0	Not cT2N0M0					
pT2N0M0	7	17	86	29	89	13	96
Not pT2N0M0	46	375					

EUS, Endoscopic ultrasound; Acc, accuracy; Sens, sensitivity; Spec, specificity; +PV, positive predictive value; –PV, negative predictive value.

*Among 445 patients with surgery first who had esophageal EUS staging.

TABLE 2. Pathologic stage groupings for 53 cT2N0M0 patients treated by surgery first

Interpretation and pathologic stage groupings	No.
Overstaged	
0	
pTisN0M0	3
I	
pT1aN0M0*	11
pT1bN0M0†	15
Correctly staged	
IIA	
pT2N0M0	7
Understaged	
IIA	
pT3N0M0	4
IIB	
pT1bN1M0	4
pT2N1M0	1
III	
pT3N1M0	7
IVB	
pT2N1M1b	1

*pT1a, intramucosal cancer. †pT1b, submucosal cancer.

Results

Errors in Clinical Staging

Of 742 clinically staged patients, 61 (8.2%) had cT2N0M0 cancer and 53 (7.1%) had surgery as first therapy. Of the 445 clinically staged patients who underwent surgery first, 24

(5.4%) had pT2N0M0 cancer. Scoring matrices and referent values for T2, N0, and T2N0M0 are listed in Table 1.

Of the 53 cT2N0M0 patients treated with surgery first, 7 (13%) were correctly staged, 29 (55%) were overstaged, and 17 (32%) were understaged (Table 2). Twenty-six overstaged patients (90%) had pT1N0M0: 11 (38%) T1a (intramucosal) and 15 (52%) T1b (submucosal). Thirteen (76%) understaged patients had pN1.

Consequences of Treating Incorrectly Staged Patients

Treatment of overstaged patients. Although survival after surgery alone of 28 overstaged patients seemed to be worse than that of 149 patients with <pT2N0M0 cancer treated by surgery alone ($P = .07$, Figure E1), this was because tumor characteristics and treatment of the groups differed. Overstaged patients had more cancers with high pT, squamous histology, and poor differentiation than the comparison group, and were more likely to have a thoracotomy (Table 3). When patients were matched, survival was similar ($P = .8$, Figure 2).

Treatment of understaged patients. Treating understaged cT2N0M0 patients by surgery alone ($n = 10$) resulted in poor survival, similar to that for 104 patients with >pT2N0M0 cancer ($P = .4$; Figure E2, Table 4), and this was also true of matched patients ($P = .4$; Figure 3, Table 4). Treating understaged patients by surgery first followed by adjuvant therapy ($n = 7$) resulted in similar intermediate survival as for 93 such patients with >pT2N0M0 cancer ($P = .5$; Figure E3, Table 5), and this was also true of matched

TABLE 3. Comparison of unmatched and matched overstaged cT2N0M0 patients

Variable	Unmatched					Matched				
	Overstaged (n = 28)		<pT2N0M0 (n = 149)		P	Overstaged (n = 25)		<pT2N0M0 (n=25)		P
	No.	%	No.	%		No.	%	No.	%	
Age (y)*	64 ± 10.7		62 ± 9.9		.4	63 ± 10.8		65 ± 8.5		.6
pT					.007					>.9
<pT1	3	11	36	24		3	12	4	16	
PT1a–lp	2	7.1	40	27		2	8.0	2	8.0	
pT1a–mm	8	29	39	26		7	28	8	32	
pT1b–inner	7	25	18	12		6	24	5	20	
pT1b–outer	8	29	16	11		7	28	6	24	
Histology					<.001					.6
Adenocarcinoma	23	82	147	99		23	92	24	96	
Squamous cell	5	18	2	1.3		2	8.0	1	4.0	
Differentiation					<.0001					.9
Undifferentiated/poor/moderately poor	13	46	20	13		11	44	10	40	
Moderate	8	29	35	23		7	28	8	32	
Moderately well/well	7	25	94	63		7	28	7	28	
Surgical approach					<.001					1.0
Thoracotomy	19	70	40	27		16	64	16	64	
Transhiatal/laparotomy	9	32	109	73		9	36	9	36	

lp, Lamina propria; mm, muscularis mucosa; inner, inner half of submucosa; outer, outer half of submucosa. *Mean ± standard deviation.

Figure 2. Comparison of survival after surgery alone in *overstaged* cT2N0M0 patients versus non-cT2N0M0 patients with <pT2N0M0 cancers (propensity-matched surgery-alone patients). Format is as in Figure 1.

Figure 3. Comparison of survival after surgery alone in *understaged* cT2N0M0 patients versus non-cT2N0M0 patients with >pT2N0M0 cancers (propensity-matched surgery-alone patients). Format is as in Figure 1.

patients ($P = .8$; Figure 4, Table 5). In understaged patients, survival after surgery and postoperative adjuvant therapy was better than after surgery alone ($P = .17$, Figure 5).

Impact of Induction Therapy

Empirical treatment of 8 cT2N0M0 patients who had induction therapy before surgery resulted in poorer survival than in those undergoing surgery first ($P = .05$, Figure 6).

Discussion

Errors in Clinical Staging

Survival of patients with cT2N0M0 and pT2N0M0 cancers is similar (Figure E4), from which one might infer that clinical staging accurately reflects pathologic staging. This is not the case; on close examination, clinical staging seems

to be nearly useless. The good survival of the majority of patients who were *overstaged* balances the poor survival of the minority of patients who were *understaged*, leading to an intermediate pT2N0M0-like survival for the group.

However, *overstaged* patients were an atypical group, composed not of a balance of patients with superficial cancer with either high-grade dysplasia or variably invasive T1 cancers,⁹ but of a majority with deeply invasive submucosal T1b cancers. We previously showed that survival is similar for such patients and those with pT2N0M0 tumors; it is worse, however, for both these groups of patients than for those with more superficial tumors.¹⁰ Thus, overstaging errors of ultrasound classification predominately occurred about the interface of the third (submucosa) and fourth (muscularis propria) ultrasound layers. Ultrasound layers

TABLE 4. Comparison of unmatched and matched understaged cT2N0M0 patients treated by surgery alone

Pathologic classification	Unmatched					Matched					P
	Understaged (n = 10)		>pT2N0M0 (n = 104)		P	Understaged (n = 9)		>pT2N0M0 (n = 9)			
	No.	%	No.	%		No.	%	No.	%		
pT					.2					1.0	
pT1b	1	10	4	3.8		1	11	1	11		
pT2	2	20	7	6.7		1	11	1	11		
pT3-4	7	70	93	89		7	78	7	78		
pN					.7					1.0	
pN0	3	30	25	24		3	33	3	33		
pN1	7	70	79	76		6	67	6	67		
pM					>.9					—	
pM0	9	90	93	90		9	100	9	100		
pM1	1	10	11	11		0	0	0	0		

TABLE 5. Comparison of unmatched and matched understaged cT2N0M0 patients treated by surgery followed by adjuvant therapy

Pathologic classification	Unmatched					Matched				
	Understaged (n = 7)		>pT2N0M0 (n = 93)		P	Understaged (n = 7)		>pT2N0M0 (n = 7)		P
	No.	%	No.	%		No.	%	No.	%	
pT					.01					1.0
pT1a	0	0	2	2.2		0	0	0	0	
pT1b	3	43	6	6.4		3	43	3	43	
pT2	0	0	4	4.3		0	0	0	0	
pT3-4	4	57	81	87		4	57	4	57	
pN					.9					1.0
pN0	1	14	15	16		1	14	1	14	
pN1	6	86	78	84		6	86	6	86	
pM					.2					—
pM0	7	100	76	82		7	100	7	100	
pM1	0	0	17	18		0	0	0	0	

are only an approximate reflection of this anatomic boundary: The third ultrasound layer is composed of the submucosa and acoustic interface between the submucosa and muscularis propria.^{11,12} Therefore, the anatomic information necessary to differentiate deep T1b submucosal cancers from more superficial T2 cancers may not be available to the ultrasonographer.

Classification errors in *understaged* patients were different. Approximately one quarter of errors were in T, one third were in N, and the remaining were in both T and N. Approximately 50% of patients with pT2 cancer have N1 regional nodal metastases.¹³ This underscores the need for improved technology to facilitate EUS fine-needle aspiration of regional lymph nodes without false-positive cytol-

ogy resulting from the sampling needle passing through the primary cancer.

These overstaging and understaging errors in classifying cT2N0M0 reflect 3 sources: 2 anatomic boundaries and regional lymph nodes. Although these errors lead to poor determination of T2N0M0 tumors, understanding their nature actually allows this inaccurate EUS information to be usefully interpreted for optimal treatment decision making.

Figure 4. Comparison of survival after surgery followed by adjuvant therapy in *understaged* cT2N0M0 patients versus non-cT2N0M0 patients with >pT2N0M0 cancers (propensity-matched similarly treated patients). Format is as in Figure 1.

Figure 5. Comparison of survival after surgery alone versus surgery followed by adjuvant therapy in *understaged* cT2N0M0 patients. At 1 and 3 years, 4 and 2 patients remained at risk in the postoperative adjuvant therapy group, with 68% confidence limits of 72% to 99% and 20% to 65% at these intervals, respectively. After surgery alone, 5 and 3 patients remained at risk, with confidence limits of 34% to 66% and 16% to 44% at 1 and 3 years, respectively. Format is as in Figure 1.

Figure 6. Comparison of survival after induction therapy followed by surgery versus surgery first in cT2N0M0 patients. At 1 and 3 years, 37 and 24 patients remained at risk in the surgery-first group, with 68% confidence limits of 84% to 73% and 47% to 61% at these intervals, respectively. After induction therapy, 4 patients and 1 patient remained at risk, with confidence limits of 32% to 68% and 1% to 24% at 1 and 3 years, respectively. Format is as in Figure 1.

Consequences of Treating Incorrectly Staged Patients

As well as being more deeply invasive, cancers of *over-staged* patients were more likely to be poorly differentiated and of squamous histology. This accounts in part for the survival difference seen in overstaged versus other patients with $\leq$ pT2N0M0 cancer. In addition, esophagectomy by thoracotomy, a predictor of worse survival in patients with superficial cancers than transhiatal resection,¹⁴ reflects our practice of performing a 2-field lymphadenectomy in patients with a high probability of regional lymph node metastases. This information is crucial for prognostication and postoperative treatment decision making and seems to be appropriate for cT2N0M0 tumors. Further, there seems to be no adverse consequences of treating overstaged cT2N0M0 patients by esophagectomy first.

Understaged patients did as poorly as other patients with $>$ pT2N0M0 cancer, a reflection of the impact of pT3 and pN1 classification on survival. However, as previously shown in matched patients, postoperative adjuvant therapy improves survival.¹⁴ Thus, consequences of understaging cT2N0M0 patients can be mitigated by accurate pathologic staging and use of adjuvant therapy after esophagectomy.

Impact of Induction Therapy

Despite the small number of patients, the association of induction therapy with the poor survival of cT2N0M0 patients is striking. This is due not only to treatment toxicity but also to cancer deaths, because 5 of 7 deaths occurred in

patients with early cancer recurrence. We know of no trial of induction therapy that includes cT2N0M0 patients, nor is such a trial likely to be conducted given the present knowledge; thus, these results should not be ignored, but they should be considered cautiously. However, even if results were at the upper confidence limits of our experience rather than the mean, there would be no survival advantage of induction therapy.

Strengths and Weaknesses

This is a single-institution study of an uncommon cancer for which treatment was nonrandomized and heterogeneous over an 18-year period. Propensity analysis was used to minimize bias.

Because the tumor is uncommon, its treatment has not been subjected, to our knowledge, to rigorous study. Until it has, we have exploited heterogeneity in treatment selection to derive a clinically logical strategy, supported by these nonrandomized data, that should minimize harm to overstaged patients while providing an effective alternative for understaged patients. Nevertheless, our protocols for managing esophageal cancer do not permit us to examine the large variety of other treatments. Some survival differences in our own treatment strategies could have been due to chance or may be real, but small sample sizes precluded all but rather large differences from being detected as distinctive. Despite practicing utmost care, clinical staging was incorrect in the majority of cT2N0M0 patients, a reflection of current technology. It is possible, but not yet demonstrated, that new generations of echoendoscopes may improve the clinical staging of patients with T2N0M0 cancers.

Treatment Algorithm

Patients with cT2N0M0 cancers should undergo surgery first, with lymphadenectomy. Clinically *understaged* patients should receive postoperative adjuvant therapy. In the unlikely event that any cT2N0M0 patients are found to have pT2N0M0 cancer, they will have acceptable survival with surgery alone; the role of postoperative adjuvant therapy is yet to be defined.

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References

1. Rice TW, Blackstone EH, Adelstein DJ, Zuccaro G Jr, Vargo JJ, Goldblum JR, et al. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. *J Thorac Cardiovasc Surg.* 2003;125:1091-102.
2. Zuccaro G Jr, Rice TW, Vargo JJ, Goldblum JR, Rybicki LA, Dumot JA, et al. Endoscopic ultrasound errors in esophageal cancer. *Am J Gastroenterol.* 2005;100:601-6.
3. Catalano MF, Sivak MV Jr, Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc.* 1994;40:442-6.
4. Rice TW, Blackstone EH, Adelstein DJ, Zuccaro G Jr, Vargo JJ, Goldblum JR, et al. N1 esophageal carcinoma: the importance of

- staging and downstaging. *J Thorac Cardiovasc Surg.* 2001;121:454-64.
5. Galen RS, Gambino SR. *Beyond Normality: The Predictive Value and Efficiency of Medical Diagnoses.* New York: John Wiley & Sons; 1975.
 6. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41-55.
 7. Blackstone EH. Comparing apples and oranges. *J Thorac Cardiovasc Surg.* 2002;123:8-15.
 8. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-81.
 9. Rice TW, Blackstone EH, Goldblum JR, DeCamp MM, Murthy SC, Falk GW, et al. Superficial adenocarcinoma of the esophagus. *J Thorac Cardiovasc Surg.* 2001;122:1077-90.
 10. Rice TW, Blackstone EH, Rybicki LA, Adelstein DJ, Murthy SC, DeCamp MM, et al. Refining esophageal cancer staging. *J Thorac Cardiovasc Surg.* 2003;125:1103-13.
 11. Kimmey MB, Martin RW, Haggitt RC, Wang KY, Franklin DW, Silverstein FE. Histologic correlates of gastrointestinal ultrasound images. *Gastroenterology.* 1989;96:433-41.
 12. Bolondi L, Casanova P, Santi V, Caletti G, Barbara L, Labo G. The sonographic appearance of the normal gastric wall: an in vitro study. *Ultrasound Med Biol.* 1986;12:991-8.
 13. Rice TW, Zuccaro G Jr, Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. *Ann Thorac Surg.* 1998;65:787-92.
 14. Rice TW, Adelstein DJ, Chidel MA, Rybicki LA, DeCamp MM, Murthy SC, et al. Benefit of postoperative adjuvant chemoradiotherapy in locoregionally advanced esophageal carcinoma. *J Thorac Cardiovasc Surg.* 2003;126:1590-6.

Discussion

Dr Steven G. Swisher (Houston, Tex). This study reviews the outcome of an uncommon subset of patients with esophageal cancer: those patients with clinical T2N0 tumors as defined by EUS. The authors make the observation that this group of patients seem to be difficult to accurately stage by EUS, with only 7 of 53 patients (13%) actually having a pathologic T2N0 tumor. Some 55% of the EUS-staged patients were overstaged and 32% were understaged, making proper treatment decisions difficult. The authors then evaluate the outcome of these patients and suggest that the optimal treatment for these patients is surgery first with postoperative chemoradiation reserved for those patients who have been understaged.

The article is to be commended for attempting to address an uncommon group of patients for whom little data are available and treatment decisions have not been defined. There are, however, several limitations to this study. It is retrospective and nonrandomized, and because of this, it is subject to bias and selection. This study was performed over a long period of time (20 years), with a small number of heterogeneous patients who were treated with several different treatment strategies. Because of these inherent limitations, accurate treatment assessments and recommendations are difficult to make even when performed with the aid of sophisticated statistical analyses.

I have several questions for the author. First, the accuracy of EUS staging for T2 esophageal cancers is much lower than that reported by recent groups who have used new EUS probes that operate at a higher frequency (15-20 MHz), as opposed to the 7.5 MHz described here, in which the esophageal wall can be visualized as a series of 7 or 9 layers. Would the use of these more accurate EUS miniprobosc eliminate some of the staging inaccuracies reported in this study?

Dr Rice. No doubt the limitation of staging is ultrasound technology. As we look at the study period, we find that staging accuracy did not get any better over time, although we do use the 12-MHz probe to look within the wall and the 7.5-MHz probe to look distantly. The problem with adding more and more layers is that you have, of course, more and more interfaces to deal with. So, although increasing technology may seem attractive, it could add more areas for error.

Dr Swisher. Second, I believe that you would agree it is difficult to come up with absolute conclusions about treatment because this is a small, retrospective, nonrandomized study performed over a 20-year time period. How did the authors select the 7 patients treated with postoperative adjuvant treatment? Was the decision made because of age or performance status or because of a feeling by the surgeon that the tumor was at high risk for recurrence?

Dr Rice. There were 8 patients over approximately 18 years who received induction chemoradiation therapy, and, yes, they probably were treated a little earlier in the series; now, we would never consider anyone with disease confined to the wall for induction therapy. Certainly in these 8 patients, there is a small amount of induction toxicity and many tumor deaths, suggesting inaccuracy in staging. That is the best we could do. I agree it is a small number, but you must realize that it took us nearly 20 years to accumulate this experience; at our institution, where we perform 80 to 100 resections a year, that is only 2 patients per year.

Dr Swisher. Third, why do the authors think that their induction therapy experience was associated with such a poor outcome in their study? At MD Anderson we reviewed 21 patients who were treated with preoperative chemoradiation and had EUS-defined T2N0 tumors. They were treated with induction chemoradiation since 1997, and their overall survival is 67% at 3 years rather than the 13% 3-year survival reported by this study. Was the increased toxicity reported by your group caused by the hyperfractionated radiation therapy and paclitaxel that were used?

Dr Rice. Only 1 of 7 deaths was due to toxicity; 6 were due to recurrent cancer.

Dr Mark J. Krasna (Baltimore, Md). Tom, as always, I compliment you and your group for helping to elucidate all of the fine intricacies in the management of esophageal cancer, the stage-specific approach.

I will just reiterate what we just heard from Dr Swisher, that to make any kind of conclusion based on 7 of 53 patients would be inappropriate when we walk out of this room, but we appreciate the chance to discuss it. I do advise more than anything to caution against what I now have heard several times as a tendency among thoracic surgeons to adopt a postoperative adjuvant therapy approach in dealing with patients with any stage of esophageal cancer. To my knowledge, there are only 2 positive trials that would support that approach. One is a Chinese trial of adjuvant radiation therapy alone for patients with esophageal cancer. The only other data that are available that are either prospective or randomized are the results of the Gastric Cancer Study, which included patients who had total gastrectomies with D1, D2 resections, radical lymphadenectomies, and most of them splenectomies. So, again, I would just caution, although I know your experience is excellent, to generalize this, that people not walk out

of the room thinking that there is a proven role for adjuvant radiation or chemoradiation for esophageal cancer.

Dr Rice. Can I turn that back to you? Where is the evidence for the benefit of induction therapy? As surgeons, I would plead with you to do the operation first whenever possible. Then at least you know the pathologic stage and can decide how to treat your patient. If you are using induction chemoradiation therapy, two thirds of your patients will not respond. That is as bad as giving them postoperative adjuvant therapy based on matched data or some questionable phase III data. But I stand, as you stand, with no phase III study to help us. So, as a surgeon, take the cancer out first. You'll be happy. At least you will know the pathologic stage.

Dr Krasna. Just to clarify, I do think that there are 3 phase III trials out there, including the first one that was presented from the group in Michigan, as well as the Walsh study and recently the Intergroup trial (CALGB 9781). Although all were small and some were questionable in terms of the long-term 5-year survival, especially for the Michigan trial, 2 of those 4 clearly showed a significant advantage in 5-year survival, not just 1-, 2-, and 3-year survivals, with trimodality therapy over surgery alone.

Dr Rice. But two thirds of your patients are getting therapy they will not benefit from: toxic high-dose therapy.

Dr Krasna. In 2 of those trials, that's correct. One of the trials was a stage-specific approach.

Dr Steven DeMeester (*Los Angeles, Calif*). I'm glad to see that your study is echoing some of the data we have presented as well, that patients, regardless of the size of the tumor (even in our experience, T3 tumors that are N0), have an excellent survival. I think that's an important message, that the lymph node status is much more important than the size of the tumor.

I am a bit surprised how 10% of patients could be overstaged when they had only high-grade dysplasia. Did those patients have a biopsy that showed cancer, leading to the EUS that gave you the misreading, or did they never have a biopsy of cancer? The question is, how did that happen?

Dr Rice. That is only 3 patients.

Dr DeMeester. That's 10% though.

Dr Rice. It's 10%, and they did have a mass in a segment of high-grade dysplasia, but the biopsy was read as invasive cancer.

Dr Antoon Lerut (*Leuven, Belgium*). You didn't say anything about the lymph node ratio. How many lymph nodes were involved and what was the ratio? Is the burden of lymph node involvement comparable to what you find in the patients with T3? Would the lymph node ratio be helpful in discriminating whether you would see that as an indication for adjuvant chemo/chemoradiotherapy?

Dr Rice. Once we find N1 disease postoperatively, we try to administer postoperative adjuvant therapy. There is no doubt that in our experience if a patient has 1 or 2 positive nodes, he or she does better than if 3 or more positive nodes are present, but that survival advantage is 10% versus 24% at 5 years. Still, if you want to leave those patients with low lymph node burden unprotected, then that would be a way to direct your postoperative adjuvant therapy.

Dr Joe B. Putnam Jr (*Nashville, Tenn*). I have no conflicts.

Tom, I appreciated the information that you presented here today and the lively discussion that has ensued.

As noted by the discussants, there are significant differences in survival that have been noted between single institutions. On the basis of multiple single-institution studies, we have created paradigms of cancer treatment, and there is a significant lack of multi-institutional trials in the prospective fashions. We have been successful in some phase II studies, and phase III studies have not been adequately subscribed to by our surgeons, medical oncologists, and radiation oncologists in a way that would allow rapid accrual, completion, and timely publication of the results. I would like your opinion as to the strategies that we can use to develop these multi-institutional trials to answer these significant problems, these significant questions that we have as surgeons and members of multidisciplinary teams in the treatment of our patients with esophageal cancer.

Dr Rice. For a phase III multi-institutional study, you obviously have to use high-volume centers. So, the first step is to get these centers to agree to participate. I believe that including low-volume centers will eliminate any survival advantage through increased operative or treatment mortality. The big boys have to get together.

Figure E1. Comparison of survival after surgery alone in *overstaged* cT2N0M0 patients versus non-cT2N0M0 patients with <pT2N0M0 cancers (unmatched patients treated with surgery alone). Format is as in Figure 1.

Figure E2. Comparison of survival after surgery alone in *understaged* cT2N0M0 patients versus non-cT2N0M0 patients with >pT2N0M0 cancers (unmatched patients treated with surgery alone). Format is as in Figure 1.

Figure E3. Comparison of survival after surgery followed by adjuvant therapy in *understaged* cT2N0M0 patients versus non-cT2N0M0 patients with >pT2N0M0 cancers (unmatched patients treated similarly). Format is as in Figure 1.

Figure E4. Survival in surgery-first cT2N0M0 patients versus patients with pT2N0M0 tumors. Format is as in Figure 1.