General Thoracic Surgery

GTS

Superficial adenocarcinoma of the esophagus

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Objective: Experience with treatment and outcome of superficial adenocarcinoma of the esophagus is limited. The purpose of this study was to evaluate the results of surgical management and identify predictors of survival.

Methods: Between September 1985 and December 1999, 122 patients underwent resection. Eighty-nine percent were men (mean age 63 ± 10 years; range 35-83 years). Sixty (49%) patients were in endoscopic surveillance programs and 48 (39%) had the preoperative diagnosis of high-grade dysplasia. Forced expiratory volume in 1 second was less than 2 L in 12 (12%). Seventy-five (61%) patients underwent transhiatal esophagectomy. Pathologic stage was N1 in 8 (7%). Pulmonary complications necessitating reintubation (respiratory failure) occurred in 10 (8%) patients. Time-related survival models were developed for decision-making (preoperative), prognosis (operative), and hospital care (postoperative).

Results: Operative mortality was 2.5%. Survival at 1, 5, and 10 years was 89%, 77%, and 68%. Preoperative decision-making factors associated with ideal outcome were 1-second forced expiratory volume of more than 2 L, surveillance, preoperative diagnosis of high-grade dysplasia, and planned transhiatal esophagectomy. Prognosis was decreased in younger patients and in those with N1 disease. Postoperative respiratory failure increased mortality.

Conclusions: Surgery is the treatment of choice for superficial adenocarcinoma of the esophagus. The ideal patient has a preoperative diagnosis of high-grade dysplasia found at surveillance, good pulmonary function, and undergoes a transhiatal esophagectomy. Discovery of N1 disease or development of postoperative respiratory failure reduces the benefits of surgery.

In the Western world, adenocarcinoma of the esophagus has one of the most rapidly increasing incidences of all carcinomas.[1,2] Preferentially it afflicts middle-aged and elderly white men. Many have long-standing reflux and usually an associated Barrett esophagus.[3] Awareness of the cancer potential in this population and emergence of endoscopic Barrett surveillance have improved detection of superficial adenocarcinoma.

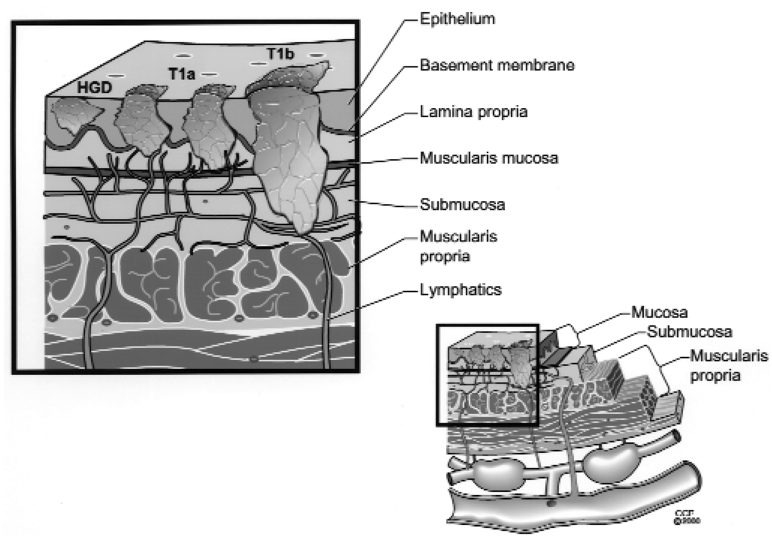

Figure 1. Superficial adenocarcinoma of the esophagus: depth of tumor invasion. The *left-hand* portion of the picture is an expanded view of a cross-section of the esophagus *(lower right). HGD,* High-grade dysplasia, which is intraepithelial carcinoma without invasion of the basement membrane; *T1a,* T1 intramucosal invasion of the lamina propria or muscularis mucosa, but not beyond; and *T1b,* T1-submucosal carcinoma with invasion limited to the submucosa.

TABLE 1. Preoperative pulmonary function

Measure	n	Mean ± SD	Range
FVC (L)	96	4.0 ± 1.0	1.7-6.0
% FVC	93	95 ± 17	47-138
FEV_1 (L)	98	2.9 ± 0.8	0.9-5.0
% FEV_1	95	87 ± 18	44-130

FVC, Forced vital capacity; % *FVC,* percent of predicted FVC based on height, sex, and age; *FEV_1,* 1-second forced expiratory volume; % *FEV_1,* percent predicted.

TABLE 2. Tumor pathology

Characteristic	No.	% of 122
T		
High-grade dysplasia	38	31
T1a	53	43
T1b	31	25
N		
N0	114	93
N1	8	7
Stage		
0	38	31
I	76	62
T1a N0	51	42
T1b N0	25	20
IIB	8	7
T1a N1	2	2
T1b N1	6	5

Superficial esophageal cancers do not invade deeper than the submucosa (Figure 1). Data concerning the treatment of these carcinomas are limited and obsolete. Extrapolation of results of surgery for advanced-stage esophageal cancer is not useful and ignores the special characteristics of this group of patients. Therefore, it is important to establish current surgical standards for the treatment of superficial adenocarcinoma of the esophagus.

The purposes of this study were to (1) evaluate the results of surgical management of superficial adenocarcinoma of the esophagus and (2) identify predictors of long-term survival for (a) decision-making (preoperative factors), (b) prognostication (operative factors), and (c) hospital care (postoperative complications).

Patients and Methods

Patients

From our prospective surgical database of 577 patients undergoing resection of esophageal carcinoma at The Cleveland Clinic Foundation beginning in January 1983, 122 patients were found to have superficial adenocarcinoma of the esophagus. Patients were not candidates if they received induction therapy for more advanced cancers that resulted in downstaging to high-grade dysplasia or T1 adenocarcinoma. The first patient presented in September 1985; patients were identified through the end of calendar year 1999. Patient ages ranged from 35 to 83 years (mean 63 ± 10 years). All were white, and 108 (89%) were men. The number of patients operated on increased across time (Appendix I and Figure 2). Preoperative pulmonary function is displayed in Table 1.

Sixty (49%) patients were in endoscopic surveillance programs (Appendix I). Eighty-nine (73%) patients had long-segment (>3

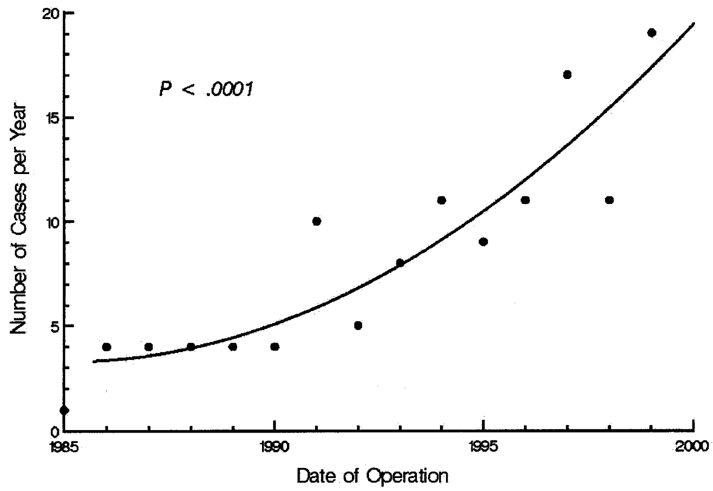

Figure 2. Accrual of cases by year of operation.

cm) Barrett esophagus. Preoperative tissue diagnosis was high-grade dysplasia in 48 (39%) patients and invasive adenocarcinoma in 74 (61%).

Surgical Approach

Transhiatal esophagectomy was done in 75 (61%) patients, thoracotomy with an abdominal incision in 46 (38%), and laparotomy in 1 (1%). Anastomosis was constructed in the neck in 101 (83%) patients and in the chest in 21 (17%). Guided by endoscopy and endoscopic ultrasound, the surgical technique evolved from routine thoracotomy to transhiatal esophagectomy with lymph node sampling for those patients with a low risk of lymph node metastases (high-grade dysplasia or T1a intramucosal cancers),[4] as illustrated by Appendix Figure I, *A* and *B* and Appendix I. Those patients in whom deeper invasion was preoperatively diagnosed underwent thoracotomy and lymphadenectomy.

Tumor Pathology

The following definitions for depth of tumor invasion were used: *high-grade dysplasia,* intraepithelial carcinoma without invasion of the basement membrane; *T1—intramucosal (T1a),* invasion of the lamina propria or muscularis mucosa, but not beyond; and *T1—submucosal (T1b),* carcinoma with invasion limited to the submucosa (Figure 1, Table 2). In 48 patients with a preoperative diagnosis of high-grade dysplasia, the esophagectomy specimens revealed high-grade dysplasia in 29 (60%), T1a N0 in 14 (29%), T1b N0 in 4 (8%), and T1b N1 in 1 (2%) patient. In 74 patients with a preoperative diagnosis of invasive carcinoma, the esophagectomy specimens revealed high-grade dysplasia in 9 (12%), T1a N0 in 37 (50%), T1a N1 in 2 (3%), T1b N0 in 21 (28%), and T1b N1 in 5 (7%) patients.

Outcomes

Postoperative complications were recorded and assessed. The latter included respiratory failure (defined as need for reintubation), aspiration, vocal cord paralysis, anastomotic leak, and wound infection (defined as infections not associated with an anastomotic leak). These complications were reviewed in detail at the time of data analyses.

Patients were followed up by periodic clinic visits; however, cross-sectional systematic follow-up was made in January 2000. Mean follow-up of all patients was 47 ± 41 months (median 38 months), with follow-up of survivors being 50 ± 41 months. Cancer recurrence, time of diagnosis, and site were recorded. A mode of death was ascertained from clinical records and reports from the families.

Data Analyses

Descriptive. Descriptive statistics are summarized as the mean and standard deviation for continuous variables and as frequencies and percentages for categorical variables. Nonparametric estimates of survival were obtained by the method of Kaplan and Meier.[5] The parametric method was used to resolve the number of phases of instantaneous risk of death (hazard function) and to estimate their shaping parameters.[6*]

Multivariable analysis

STRATEGY. The strategy for the multivariable analysis used a sequential approach to variables that reflects the purposes of the study.

DECISION-MAKING. Preoperative variables and those reflecting the operative strategy (transhiatal vs thoracotomy approach, construction of the anastomosis in the neck or chest), which would be determined preoperatively, were examined. This was labeled the *decision model.*

PROGNOSTICATION. Tumor pathologic variables were added to the preoperative candidate variables to refine patient prognosis. The preoperative diagnostic variables were not retained in this analysis. This was labeled the *prognostic model.*

HOSPITAL CARE. In addition to the aforementioned variables, the influence of postoperative complications was examined, recognizing that these followed "time zero" but preceded the dominant late hazard phase. This was labeled the *hospital care model.* To supplement this latter model, multivariable logistic regression was

[*]Available by anonymous ftp from ftp://uabcvsr.cvsr.uab.edu.

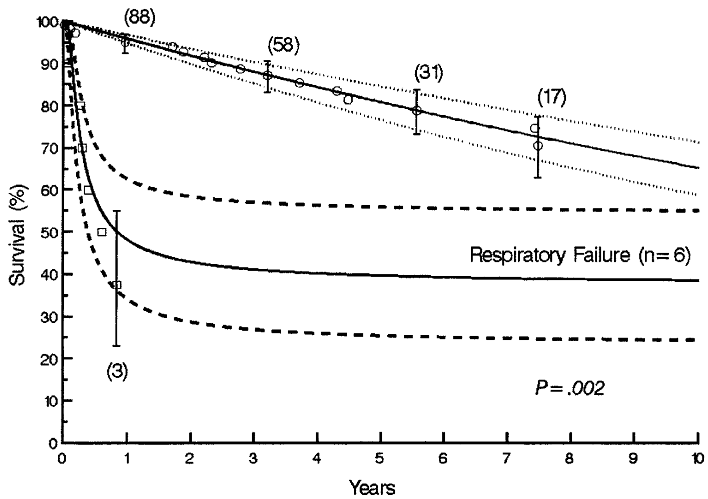

Figure 3. Survival stratified according to patients not experiencing postoperative respiratory failure *(open circles)* compared with patients experiencing respiratory failure *(open squares).* The number of patients at risk at various time points is given along with confidence limits equivalent to 1 standard deviation (see "Patients and Methods").

also used on the complications themselves to identify factors predisposing patients to their occurrence.

Because the surgical technique and decision-making changed across time (Appendix I) and simultaneously early mortality improved (P = .01), we analyzed the potentially confounding trends across time to identify if possible those changes that improved results. The multivariable analyses presented all account adequately for the information attributable to the date of operation. These models include factors whose prevalence changed across time. Strategically, we believe that such models are desirable and more helpful than simply attributing the improvement in results to a so-called learning curve.

VARIABLE SCREENING. Initial screening of variables possibly related to survival used the log-rank test and the Cox proportional hazards model. The potential risk factors (variables) were organized for analysis as in Tables 1 to 3. Continuous and ordinal variables were assessed univariably by decile risk analysis to suggest transformations of scale to incorporate into the multivariable analyses to ensure that the relation of these variables to outcome was well calibrated with respect to model assumptions. Informative imputation for missing values of pulmonary function tests used a multiple regression model based on available function tests, age, and sex.

VARIABLE SELECTION. For each of the 3 hazard models, multivariable survival analysis was performed for each hazard phase using a directed technique of entry of variables into the multivariable models.[7] However, the early hazard phase, determined from the data, was calculated to contain only 5 events; thus, there was limited ability to identify early-phase risk factors.

A P = .1 criterion for retention of variables in the final models was used. Because of small study size, bootstrap resampling was used to validate the models.[8] Further details of this method are supplied in Appendix II. Thus, the risk factors were not only identified as statistically significant by traditional analysis, but also occurred the most frequently in bootstrap analysis. The tables of risk factors include frequency of occurrence from multivariable bootstrap modeling, as well as conventional magnitude and certainty of the association.

Presentation. Because fewer than 10 percent of the patients were followed up longer than 10 years, all graphic presentations are truncated at 10 years.

Confidence limits (CL) of proportions are also equivalent to 1 standard error (68% CL).

Tables of risk factors identified in the hazard domain are presented with their regression coefficients rather than hazard ratio, because the model is not one of proportional hazards. Instead, because the hazard function multivariable analyses are completely parametric (generate an equation), "nomograms" from the analyses are presented in which specific values are entered into the equations, the equations solved, and the results presented graphically with confidence limits.

Results

Evaluation of Surgical Results

There were 3 operative deaths. Two patients died in the hospital after the operation and 1 within 30 days, for an operative mortality of 2.5% (CL 1.1%-4.9%). Three additional deaths, 2 from respiratory complications and 1 from gastrointestinal bleeding, occurred in the first 6 months.

Important postoperative morbidity included wound infections not associated with anastomotic leak in 18 (15%) patients, anastomotic leak in 16 (13%) patients, respiratory failure requiring reintubation in 10 (8%) patients, vocal cord paralysis in 8 (7%) patients, and clinically important aspiration in 6 (5%) patients. The occurrence of wound infections was consistent across time (P = .4). Anastomotic leaks occurred similarly when the anastomosis was constructed in the chest (4/21 patients, 19%) or in the neck (12/101 patients, 12%), P = .4. The occur-

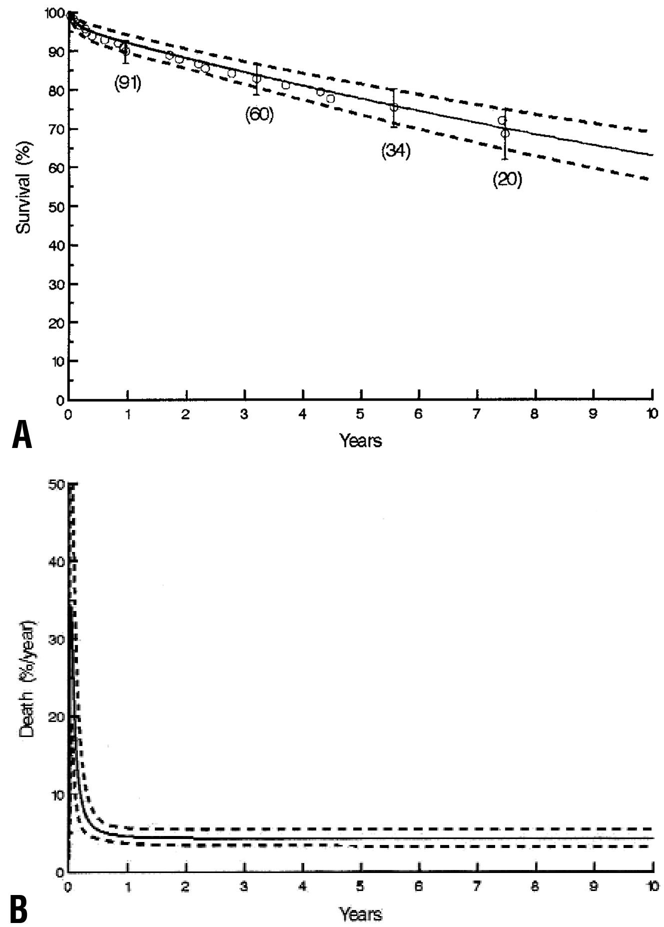

Figure 4. Survival after operation. Nonparametric Kaplan-Meier time-related estimates are presented as open circles accompanied by asymmetric confidence limits equivalent to 1 standard error. The smooth solid curve is the completely independent parametric estimate of the distribution of intervals to death. These are accompanied by confidence limits equivalent to 1 standard error. The numbers in parentheses represent the number of patients being followed up at that point in time. A, Survival. B, Hazard function.

rence of respiratory failure requiring reintubation dramatically fell during the 1980s (Appendix I, Appendix Figure I, *C*); thus, it occurred more often after thoracotomy (8/46 patients, 17%) than after a transhiatal approach (2/75 patients, 3%), $P = .006$. Survival was importantly diminished in patients experiencing the complication of respiratory failure (Figure 3). With increasing experience, there was a general decline in the occurrence of any complication ($P = .03$) and particularly of those other than wound infections ($P = .008$, Appendix Figure I, *D*).

Overall survival, including operative deaths, was 89%, 77%, and 68% at 1, 5, and 10 years after the operation (Figure 4, *A*). The instantaneous risk of death was high immediately after the operation, then fell to a constant level of 4.2% per year (CL 3.3%-5.4%) by about 6 months postoperatively (Figure 4, *B*).

Thirteen patients died of cancer. Three died with locoregional recurrence and 10 with distant metastases. There were 6 noncancer deaths.

Predictors of Survival

Variables individually associated (univariable) with time-related, all-cause mortality included older age, lower values of pulmonary function tests, lack of endoscopic surveillance, increasing depth of tumor invasion, regional lymph node metastasis, and operation earlier in the experience (Table 3).

Decision model. Low forced expiratory volume in 1 second (FEV_1), unindexed to sex, age, and size, was a risk factor for early death (Table 4). Risk became evidently different (defined as non-overlapping confidence limits compared with the normal value) only for FEV_1 values under about 2 L (Figure 5).

TABLE 3. Univariable Cox models

Variable	Hazard ratio	95% CL	*P* value
Demographic			
Sex			
Male/female	0.94	0.22-4.1	.9
Age at operation			
Per 10-year increase	1.90	1.19-3.0	.007
History and preoperative findings			
Barrett surveillance			
Yes/no	0.28	0.11-0.70	.007
Barrett length			
>3 cm/0-3 cm	0.53	0.24-1.21	.13
Preoperative diagnosis			
T1 vs high-grade dysplasia	2.6	1.01-6.5	.05
Pulmonary function			
FEV_1			
Per liter increase	0.19	0.08-0.45	<.001
< 2L/> 2L	7.6	2.3-24	<.001
Pathology			
T stage			
T1a vs high-grade dysplagia	1.96	0.60-6.4	.3
T1b vs high-grade dysplagia	4.6	1.48-14.3	.008
N stage			
N1/N0	6.4	2.3-17.6	<.001
Year of operation			
Per 1-year increase	0.87	0.78-0.97	.02
Hospital complications			
Wound infection			
Yes/no	1.02	0.34-3.0	.97
Anastomotic leak			
Yes/no	1.09	0.37-3.2	.9
Respiratory failure			
Yes/no	4.1	1.59-10.5	.004
Vocal cord paralysis			
Yes/no	0.51	0.07-3.8	.5
Aspiration			
Yes/no	2.1	0.62-7.2	.2

CL, Confidence limits.

Late survival was best for patients in an endoscopic surveillance program, those with high-grade dysplasia rather than invasive adenocarcinoma on preoperative biopsy, and for patients who underwent a transhiatal esophagectomy (Table 4). These variables are reasonably secure because their frequency of occurrence by bootstrap resampling was greater than 50% except for preoperative tumor diagnosis. Figure 6 represents 2 solutions, the best and the worst, of the decision model ("nomogram," see "Patients and Methods").

Prognostic model. The addition of pathologic stage to the decision-model variables refined the patients' prognoses. N1 disease was the most powerful predictor of long-term prognosis (Table 5). Although depth of tumor invasion (T) was univariably related to prognosis (Figure 7), its importance was overwhelmed in the analysis by the presence of N1 disease (Figure 8). The accuracy of this model is corroborated by the comparison to actual deaths; from the parametric model, we predict 5.6 deaths among the patients with high-grade dysplasia versus 4 actual ($P = .5$), 9.3 deaths among T1a patients versus 9 actual ($P = .9$), and 10.1 deaths among T1b patients versus 12 actual ($P = .5$) (Appendix Figure III).

After accounting for pathologic stage, age at operation became a risk factor. No sharp age cutoff was identified: the older the patient, the shorter the survival. However, patients younger than 55 years had poorer survival than their US population counterparts, whereas patients aged 55 to 75 and

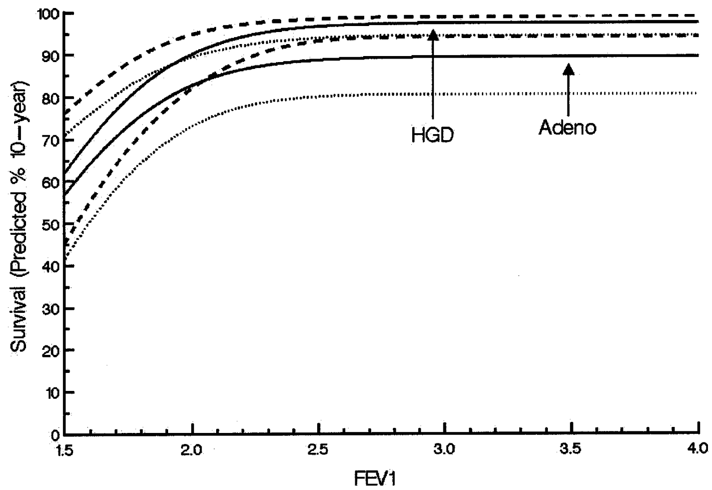

Figure 5. Ten-year survival according to FEV_1 in 2 patients. One patient has high-grade dysplasia *(HGD)* on preoperative biopsy and the other invasive adenocarcinoma (*Adeno*). Both patients are in a Barrett surveillance program, and both would have a planned transhiatal esophagectomy. The depiction represents 2 solutions of the decision model (Table 4). Note the evident differences (nonoverlapping lower and upper confidence limits) below FEV_1s of approximately 2 L.

TABLE 4. Risk factors for death: decision model

Variable	Coefficients ± SD	*P* value	Frequency*
Early postoperative hazard phase			
Low FEV_1	−1.01 ± 0.38†	.008	93%
Late hazard phase			
Not in surveillance program	1.40 ± 0.57	.01	72%
Invasive adenocarcinoma‡	1.43 ± 0.64	.03	35%
Intended surgical approach: thoracotomy	1.34 ± 0.57	.02	64%

FEV_1, One-second forced expiratory volume; *SD,* standard deviation.
*Frequency of appearance in 1000 bootstrap analyses (see "Patients and Methods").
†$[FEV_1]^2$ squared transform.
‡Preoperative diagnosis.

those more than 75 years lived about as long as expected (Appendix Figure IV).

Hospital care model. The addition of postoperative complications identified respiratory failure as a predictor of early mortality (Table 6, Figure 3).

Discussion

Once rare, superficial adenocarcinoma of the esophagus is being seen more often in clinical practice. The changing epidemiology of esophageal carcinoma, partly due to the increasing incidence of Barrett esophagus in middle-aged and elderly white men, accounts for this. Superficial adenocarcinoma of the esophagus does not invade deeper than the submucosa. A controversy is the inclusion of high-grade dysplasia in this entity. High-grade dysplasia has cytologically malignant cells that have not breached the basement membrane and invaded the lamina propria. Presently, it is impossible to predict which cases of high-grade dysplasia will progress, and at what rate, to invasive cancer. Further, preoperative biopsy is unable to define this group reliably. In our experience, 40% of patients with a diagnosis of high-grade dysplasia have invasive cancer. Therefore, because of the difficulty in its diagnosis and definition, we have included high-grade dysplasia in this report.

Superficial adenocarcinoma of the esophagus is a potentially curable cancer. Patients with the earliest-stage cancers, high-grade dysplasia, or invasion of the mucosa (T1a) and without regional lymph node metastases (N1) have the best outcome. Patients in endoscopic surveillance programs are those most likely to exhibit favorable pathologic findings. However, patients not in surveillance programs and those who have invasive cancer on preoperative biopsy still may benefit from surgery.

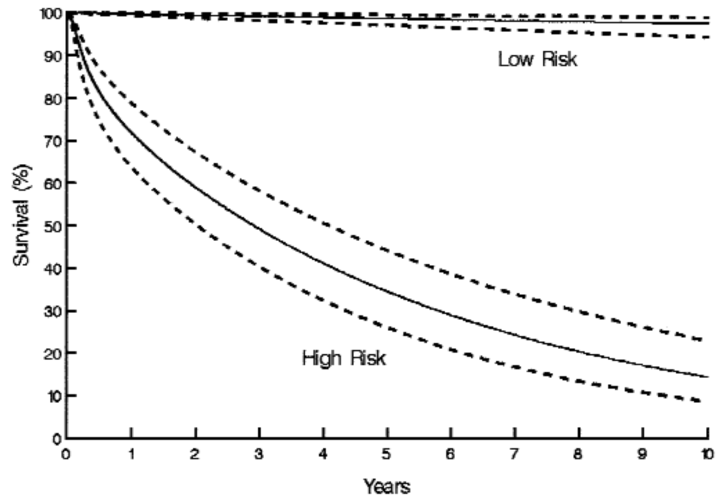

Figure 6. Ten-year predicted survival in a low- and high-risk patient. The low-risk patient has an average FEV_1 of 3 L, is in a Barrett surveillance program, and has high-grade dysplasia on biopsy; a transhiatal approach is planned. The high-risk patient has an FEV_1 of 175 L, is not in a Barrett surveillance program, and has invasive adenocarcinoma on biopsy; a thoracotomy is planned.

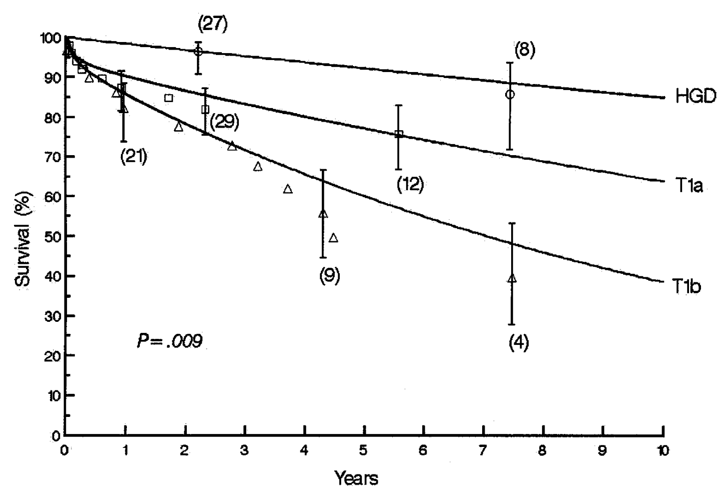

Figure 7. Survival stratified according to depth of tumor invasion *(T). HGD,* High-grade dysplasia.

The decision for surgery needs to include careful pulmonary assessment. An absolute FEV_1 of more than 2 L predicts improved outcome. If thoracotomy is avoided and a transhiatal approach is used, long-term survival is better for all patients with superficial adenocarcinoma of the esophagus.

The surgical extreme is thoracotomy with 3-field lymphadenectomy.[9] However, this puts the majority of patients at risk of increased morbidity and mortality with questionable gain.[10] Lymphadenectomy and its extent are controversial, especially in superficial cancers; by avoiding thoracotomy through the use of transhiatal esophagectomy and substituting lymph node sampling for lymphadenectomy, our study demonstrates a survival advantage. The finding of regional lymph node metastasis (N1) at operation is ominous and the most powerful determinant of prognosis. The lymphatic anatomy, which is peculiar to the esophagus, links depth of tumor invasion to regional lymph node status (Figure 1). Although considered independent factors in staging,[11] T and N are interrelated.[4] In superficial adenocarcinoma of the esophagus, as in advanced-stage cancer, the presence of N1 disease overwhelms depth of tumor invasion (T) in prognosis.[12] The effect of age is paradoxic. Although increased age is associated with decreased survival, the long-term benefit of this operation is greatest to the elderly. Compared with equivalent-aged cohorts, younger patients do worse. Therefore, older patients should not be denied surgery.

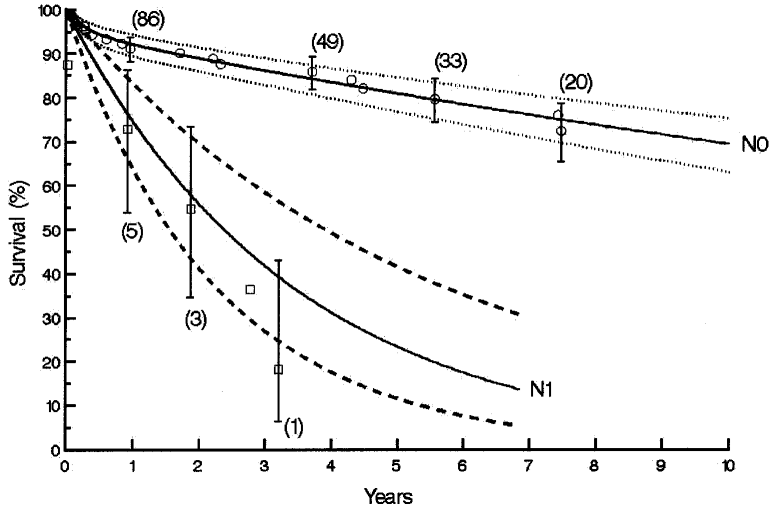

Figure 8. Survival stratified according to the presence *(N1)* or absence *(N0)* of positive lymph nodes.

TABLE 5. Risk factors for death: prognostic model

Variable	Coefficients ± SD	*P* value	Frequency*
Early postoperative hazard phase			
Low FEV_1	–1.05 ± 0.41†	.01	86%
Late hazard phase			
Old age	0.76 ± 0.32	.02	53%
Not in surveillance program	1.38 ± 0.58	.02	69%
N1 disease	2.2 ± 0.55	<.0001	66%
Thoracotomy	1.33 ± 0.58	.02	72%

FEV_1, One-second forced expiratory volume; *SD,* standard deviation.
*Frequency of appearance in 1000 bootstrap analyses (see "Patients and Methods").
†$[FEV_1]^2$ squared transform.

TABLE 6. Risk factors for death: hospital care model

Variable	Coefficients ± SD	*P* value	Frequency*
Early postoperative hazard phase			
Low FEV_1	–0.83 ± 0.42†	.05	80%
Late hazard phase			
Old age	1.03 ± 0.35	.004	53%
Not in surveillance program	1.91 ± 0.62	.002	64%
N1 disease	2.7 ± 0.58	<.0001	65%
Thoracotomy	1.18 ± 0.60	.05	71%
Postoperative respiratory failure	2.8 ± 0.63	<.0001	40%

FEV_1, One-second forced expiratory volume; *SD,* standard deviation.
*Frequency of appearance in 1000 bootstrap analyses (see "Patients and Methods").
†$[FEV_1]^2$ squared transform.

Careful preoperative selection and meticulous operative management do not guarantee excellent outcome and may be thwarted by postoperative complications. Improved hospital care, which includes aggressive pulmonary hygiene, prevention of aspiration, treatment of vocal cord neurapraxia, and avoidance of early feeding, likely accounts for the decrease in respiratory complications in this group as experience accumulated.

Recently, alternative therapies for superficial adenocarcinoma of the esophagus have been proposed. They are mucosal ablation and endoscopic mucosal resection. Ablation eliminates pathologic review of the mucosa and prohibits the detection of submucosal invasion and lymphatic spread. If ablation depth is adequate, complications such as stricture and perforation increase.[13] Furthermore, ablation may be incomplete, and submerged Barrett epithelium will be hidden from further surveillance.[14-16]

In theory, endoscopic mucosal resection is far more appealing. The ability to inspect the resected specimen allows determination of depth of invasion and detection of lymphatic invasion. If pathologic review is favorable and only high-grade dysplasia is found, esophagectomy may be avoided. However, early experience with endoscopic mucosal resection has been disappointing, with cancer recurring in 17% of patients within an average follow-up of 12 months.[17] After endoscopic mucosal resection, repopulation of the esophageal mucosa with squamous epithelium may be possible if gastroesophageal reflux is avoided. Acid suppression may be difficult in patients with Barrett esophagus.[18-20] Surgical experience suggests that patients with Barrett esophagus are more likely to have a short esophagus, require complex surgical repairs, and have worse acid control than patients without Barrett esophagus.[21,22]

Resection for superficial esophageal carcinoma with low morbidity and mortality is the challenge to surgeons. From our experience, this requires meticulous patient selection and preparation and a significant experience with esophageal surgery. The patient with impaired respiratory function should be carefully considered and perhaps denied resection. Because these tumors are early stage, there is time for pulmonary preparation, smoking cessation, and weight loss. Impeccable surgical technique and prevention of postoperative complications should minimize early operative morbidity and deaths. It is the surgeon's responsibility to achieve the patient's optimal condition. Unlike the majority of patients with esophageal carcinoma, these patients have the potential for long-term survival.

Although this study of a previously uncommon patient population is seemingly large, in reality, it is small and not randomized. However, the results strongly suggest that endoscopic surveillance of patients with Barrett esophagus and early intervention before the tumor invades deeply or involves lymphatics provide the best long-term results. Alternative therapy should be reserved for patients who are not candidates for esophagectomy.

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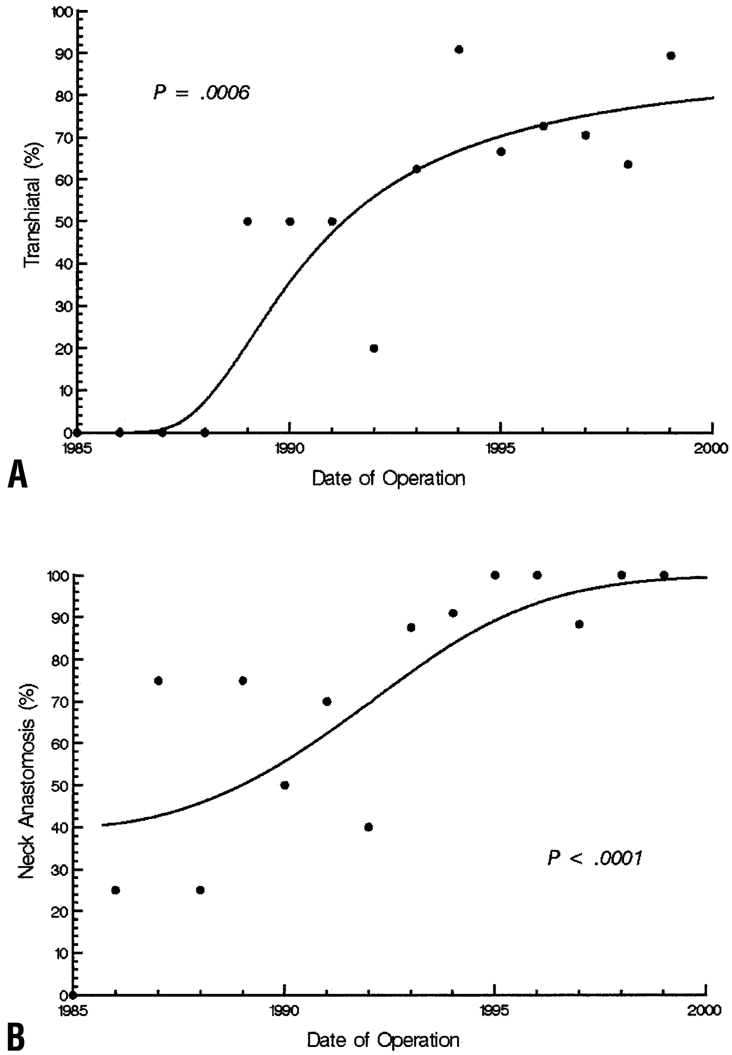

Appendix Figure I. Time trends. A, Percent of patients undergoing a transhiatal esophagectomy. B, Percent of patients whose anastomosis was in the neck.

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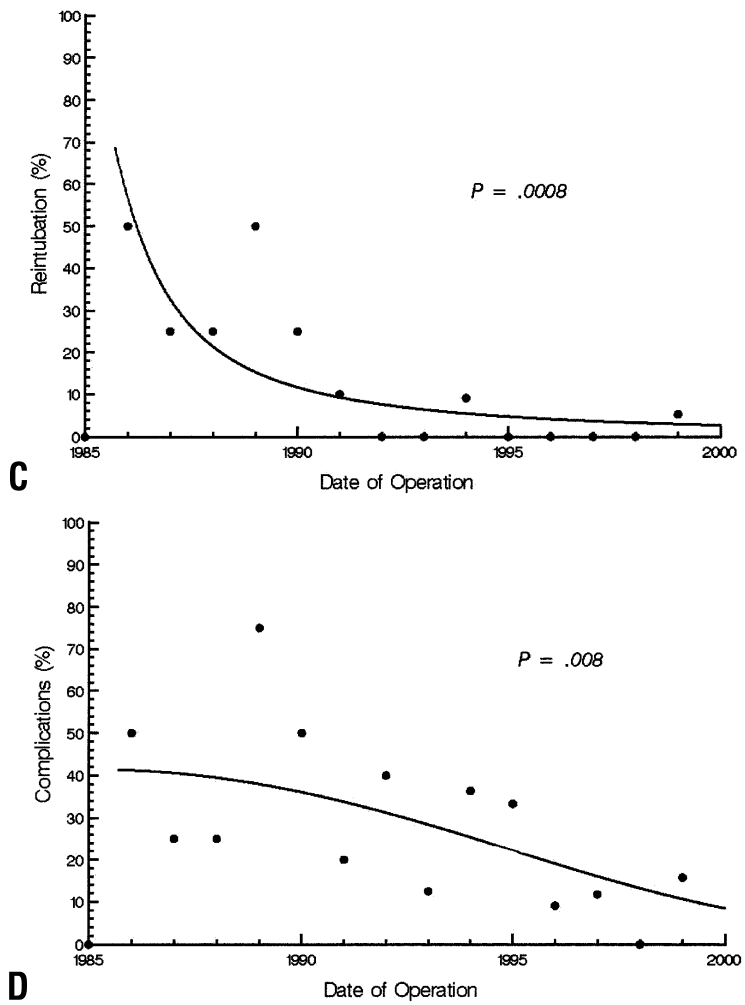
Appendix I. Trends Across the Experience

Changing prevalence of preoperative patient and disease characteristics, operative technique, and postoperative complications across the surgical experience were characterized by means of logistic regression for binary variables and linear regression for continuous variables. The calendar date of operation was expressed as a continuous interval since January 1, 1985. Logarithmic, inverse, and power transformations were used to best characterize the information. Trends found to be significant over time are presented in Appendix Figure I. A nonsignificant ($P = .3$) trend was the increase in prevalence of patients in endoscopic surveillance programs.

Appendix II. Variable Selection Criterion and Model Validation

The *P* value for reduction of variables in the final model was liberal because of the high possibility, given the small number of deaths, that important variables related to survival would be overlooked by too stringent a variable retention criterion (type II error). The variable selection criteria exposed us to the risk of model overdetermination, whereby risk factors cease to be general common denominators and become identifiers of specific individuals in the data set that have died (type I error). Therefore, to balance these errors, all multivariable analyses were supplemented by bootstrap resampling variable selection.[7,23] For this, 1000 samples of the data set were drawn with replacement, and an automated stepwise variable selection was performed with an entry criterion of $P = .12$ and a retention criterion of $P = .1$. For clusters of highly correlated variables, such as all transforms of the same or similar variables (pulmonary function tests, age, date of operation) or for closely related variables (surgical approach and location of esophageal anastomosis, the variables identifying depth of tumor invasion), only 1 member of each cluster was allowed to be entered. By this strategy, the frequency of occurrence of variables within each cate-



Appendix Figure I. Cont'd. Time trends. C, Percent of patients requiring postoperative reintubation for respiratory failure. D, Percent of patients experiencing an important surgical complication other than wound infection.

gory yielded an accurate assessment of the likelihood that 1 variable from that cluster should belong in the final model.

Appendix III. Adequacy of the Prognostic Model (Table 5)

To better understand the analyses, particularly with respect to the high correlation among variables that can give rise to equivalent but different models,[24] we solved the prognostic equation for the characteristics of each patient in the study.[25,26] This produced an individualized survival curve for each patient. The patients were then stratified according to depth of tumor invasion, a variable not in the risk factor model. The curves were averaged within each stratum and compared with the Kaplan-Meier estimates.

Appendix Figure III indicates that the model is sufficient for prognostication, despite not containing information directly about depth of tumor invasion.

Appendix IV. Survival Compared with Matched US Population

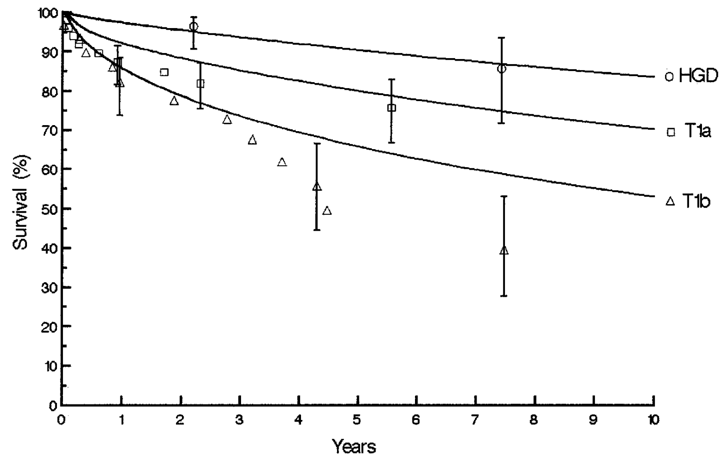
For informal comparison, a predicted population survival curve was generated for each patient using (a) age at operation, (b) sex, and (c) race. These curves were averaged within strata to yield a comparative population life table.

Discussion

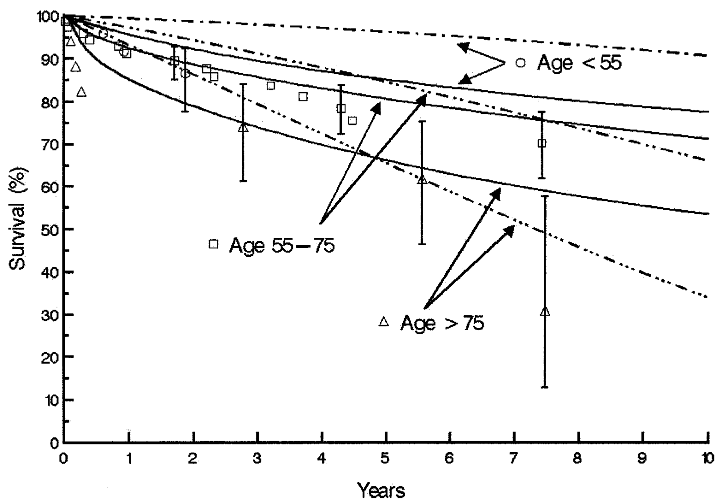
Dr Nasser K. Altorki *(New York, NY).* I congratulate Dr Rice and his colleagues on bringing to us what is probably the largest series of superficial adenocarcinoma in the United States, and probably in Europe as well.

You have reaffirmed 2 of our commonly held beliefs. One is that an endoscopic diagnosis of high-grade dysplasia warrants an esophagectomy. The incidence of cancer in your series is about 40%, much like the incidence reported by others. The second is that patients who are enrolled in an endoscopic surveillance program generally present with earlier stage disease and generally have a better outcome, and I believe that to be true.

I have 2 comments and 2 questions. In the manuscript as well as in the presentation, there was almost a synonymous use of the words high-grade dysplasia and cancer. I believe that once high-grade dysplasia is confirmed in the resection specimen, it should not be included in further analysis, particularly the survival analy-



Appendix Figure III. Kaplan-Meier estimates of tumor invasion as in Figure 3. The *solid curves* are predicted from the prognostication model (Table 5). The inference from this depiction is that the model is sufficient for prognostication, even though it does not contain information directly about depth of tumor invasion. Patients with high-grade dysplasia are well represented by the *smooth upper curve,* as are patients with T1a tumors by the *second curve.* After about 3 years, patients with T1b tumors fare worse than predicted, but the number of patients at that point is so small that this additional variable did not provide significant information.



Appendix Figure IV. Survival within age groups compared with a matched US population. The *dot-dash curve* is the matched survival among patients less than 55 years of age. The *dash-dot-dot-dash curve* is the population life table for patients between the ages of 55 and 75 years. The lowest *dash-dot-dot-dash curve* is for the matched population more than 75 years of age.

sis of patients with invasive cancer. High-grade dysplasia is a marker of associated invasive carcinoma, it is a preneoplastic lesion, but, as you know, there is sufficient controversy about its final outcome that I do not think it should be equated with cancer.

You have concluded that an FEV_1 of less than 2 L and respiratory failure requiring reintubation both portend a poor outcome. I understand that Dr Blackstone has applied quite a bit of statistical firepower to this manuscript, and I am not going to challenge that. However, I note that there were 12 patients who had an FEV_1 of less than 2 L in the whole group, probably about 10%, and 10 patients who required reintubation. I am hesitant to accept that recommendation given the small numbers involved, and I wonder whether that conclusion can be tempered.

I have 2 questions. You have stated that transhiatal esophagectomy is associated with a good outcome. We are all aware that stage is the most important determinant of outcome, not particularly where the surgeon places his incision. Would you care to elaborate, Dr Rice, on the factors that influence the choice of your surgical incision? Is it possible that there was some inherent selection bias that affected the use of a transthoracic approach?

The second question pertains to the survival figures presented. I think the survival for stage T1a was 80%, and that is a reasonable survival figure. Survival for T1b was about 50%. In our experience, that number should probably be in the 70%-plus range. Is it possible that some of these patients were understaged primarily by the use of a transhiatal or a less extensive lymph node dissection? I am aware of your support for lymph node dissection. How do you go about resecting lymph nodes for esophageal cancer?

Dr Steve R. DeMeester *(Los Angeles, Calif).* Did you look at the depth of tumor invasion independent of lymph node involvement? One thing that we have come to realize is that intramucosal cancers are rarely associated with lymph node metastases. Is that the same in your experience? In other words, how many intramucosal cancers had lymph node metastases?

Next, is reintubation really a marker of sepsis, graft failure, or graft leak and is that what you are looking at, or is the intubation itself somehow important in the decrement in survival in these patients?

Last, getting back to the issue of whether intramucosal cancers are associated with lymph node metastases or not, it has been our experience that they are not associated with lymph node metastases. Therefore, we can offer these patients an operation that we think is an even better reconstruction, the vagus-sparing esophagectomy. This procedure preserves the vagus nerves, strips the esophagus out of the mediastinum, and is even less invasive than the transhiatal approach. Have you had any thoughts in those directions?

Dr Bruce J. Leavitt *(Burlington, Vt).* Knowing your results in the high-risk category and based on your results in this report, have you considered other forms of therapy for high-grade dysplasia of the distal esophagus?

Dr Reginald V. Lord *(Los Angeles, Calif).* What was the cause of death in the patients with high-grade dysplasia? Specifically, did any of them have cancer deaths?

Dr Rice. I would like to thank Dr Altorki for his comments. They will be considered in the revision of the manuscript.

Your first question: What are the factors that determined whether a patient would have a transhiatal esophagectomy? One factor is my maturation as a surgeon. I became more comfortable over time with transhiatal esophagectomy and I came to appreciate the improvement in the patient's recovery. My learning curve no doubt affects the study.

The question about survival: In the T1a group 5-year survival is 80%, and in the T1b group it is only 50%. It is interesting that of the 13 cancer deaths, only 3 were due to local recurrence and 10 were from distant spread. This tells something about the efficacy of the operation and the lack of an understaging effect that may have existed because of the transhiatal approach. I would like to point out that there are 3 lymphatic routes by which this tumor can metastasize: It can spread along the submucosal lymphatics; in 10% of the patients it may spread directly into the thoracic duct; and in the rest of the patients it will metastasize to regional lymph nodes. This cancer can spread very early, and it can involve distant sites before it spreads to regional lymph nodes. The rapid decrease in survival with minimal increase in tumor invasion reflects the possibility of distant spread without N1 disease.

Dr DeMeester, 5% of our patients with intramucosal cancer had regional lymph node metastases. This is the result of the lymphatic anatomic peculiarity of the esophagus. There are lymphatics in the muscularis mucosa and lamina propria. Twenty-five percent of our patients with submucosal cancer had regional lymph node metastases. This is less than your reported experience of 50% prevalence of N1 disease in submucosal tumors. This may reflect our use of transhiatal esophagectomy and your use of a rigorous lymphadenectomy, lymph node sampling versus lymphadenectomy.

Reintubation, no doubt, reflects complications that result in respiratory failure, graft failure, aspiration pneumonia, adult respiratory distress syndrome, and other problems. Reintubation is a marker. If a patient has to be reintubated, the cause of that problem must be identified.

This paper is interesting because it separates the disease from the operation, because the survival is so good. If one can avoid a thoracotomy, the patient may do better. If an even less invasive operation than transhiatal esophagectomy can be done, the results may even be better.

About other forms of treatments, the 2 forms of treatment that you are suggesting are mucosal ablation and endoscopic mucosal resection. Mucosal ablation is a bad procedure in these patients, because it ablates the findings we want to follow to identify progression to cancer. It may also bury the columnar epithelium under a pseudosquamous epithelium. Surveillance in these patients will be inadequate. We have seen patients with Barrett adenocarcinoma buried under this pseudosquamous epithelium. Endoscopic mucosal resection is much more appealing. However, a recent report shows a 17% recurrence of cancer within a 12-month follow-up in patients undergoing endoscopic mucosal resection. In this group of patients with an excellent prognosis with resection, we should look at ways to decrease the morbidity of esophagectomy.