Effect of Barrett's esophagus surveillance on esophageal preservation, tumor stage, and survival with esophageal adenocarcinoma

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Objectives: Surveillance endoscopy has been recommended for patients with Barrett's esophagus; however, recent studies have questioned the importance owing to the new, lower, estimates of the rate of progression of Barrett's esophagus to cancer. The aim of the present study was to compare the tumor stage, survival, and frequency of esophageal preservation in patients who presented with progression of Barrett's esophagus within a surveillance program versus those who presented with prevalent disease.

Methods: A retrospective chart review was performed of all patients treated for high-grade dysplasia or esophageal adenocarcinoma from 2005 to 2010. The surveillance group included patients who had had at least 1 endoscopy and biopsy confirming intestinal metaplasia (with or without low-grade dysplasia) 6 months or more before the endoscopy showing progression.

Results: A total of 224 patients were included in the present study, 36 in the surveillance group and 188 in the prevalence group. The surveillance patients had significantly earlier stage tumors ($P < .0001$) and were more likely to undergo endoscopic therapy and to keep their esophagus (44% vs 11%, $P < .0001$) than were patients with prevalent disease. Furthermore, the patients in the surveillance group were less likely to have lymph node metastases and had better overall and disease-free survival. No patient with high-grade dysplasia or an intramucosal tumor died of cancer.

Conclusions: Patients within a surveillance program for Barrett's esophagus had better survival and were less likely to have an esophagectomy than those who presented with prevalent disease. Treatment of intramucosal cancer was curative, and improved survival with surveillance was not secondary to lead time bias. Surveillance endoscopy remains important in patients with Barrett's esophagus. (J Thorac Cardiovasc Surg 2013;146:31-7)

Esophageal adenocarcinoma is 1 of the world's deadliest cancers, with a 15% overall 5-year survival rate. The major risk factor for esophageal adenocarcinoma is Barrett's esophagus (BE). The development of adenocarcinoma from BE is known to occur through a series of histologic changes in the metaplastic epithelium, starting with dysplasia and ending with invasive cancer. Surveillance endoscopy has been recommended for patients with BE to allow the detection of progression and treatment at a curable stage of the disease. However, several recent studies have suggested that the risk of progression in patients with BE is lower than previously reported, have questioned the value of surveillance endoscopy, and have promoted a laissez-faire attitude toward BE.^{1,2} Concurrent with these reports have been studies indicating that patients with BE and high-grade dysplasia (HGD) or intramucosal adenocarcinoma can often be

successfully treated endoscopically, with preservation of their esophagus.^{3,4} In contrast, esophagectomy, usually combined with neoadjuvant chemoradiotherapy, is required to treat patients with more advanced tumors. The aim of the present study was to compare the tumor stage, survival, and frequency of esophageal preservation between patients who presented with progression of BE within a surveillance program and those who presented with prevalent disease outside of a surveillance program.

METHODS

Patients

We reviewed the records of all patients treated with endotherapy or esophagectomy for HGD or esophageal adenocarcinoma by the thoracic surgery division from 2005 to 2010. We selected 2005 for the start of the study because, by that point, endoscopic therapy with both endoscopic resection and ablation was well established at our center. The patients were considered to be under surveillance if they were aware of their diagnosis of BE and had had at least 1 endoscopy and biopsy confirming intestinal metaplasia (with or without low-grade dysplasia) a minimum of 6 months before the endoscopy showing disease progression to either HGD or invasive adenocarcinoma (surveillance group). The surveillance group was compared with patients found at index endoscopy to have either HGD or invasive adenocarcinoma (prevalence group). The institutional review board of the University of Southern California approved the study.

Endoscopic Therapy Versus Esophagectomy

Upper endoscopy was performed by the attending thoracic surgeon in all patients before deciding on the type of therapy. Patients with HGD or

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Abbreviations and Acronyms

BE = Barrett's esophagus

HGD = high-grade dysplasia

a biopsy diagnosis of adenocarcinoma, in whom Barrett's mucosa was completely flat without any nodules or lesions, were eligible for ablation with radiofrequency energy using the Halo 360° or 90° device (BARRX Medical, Covidien, Mansfield, Mass). In patients with HGD or a biopsy finding showing adenocarcinoma, in whom Barrett's mucosa showed an ulcer or lesion of any type, endoscopic resection of the lesion was performed to pathologically determine whether cancer was present and, if so, the depth of invasion. Patients with tumors invasive beyond the muscularis mucosa into the submucosa were not eligible for endoscopic therapy or vagal-sparing esophagectomy. These patients were advised to undergo esophagectomy with lymph node dissection, most commonly using an en bloc technique. If the lesion was confirmed to be intramucosal by endoscopic resection, the patients were eligible for endoscopic therapy or vagal-sparing esophagectomy. The decision between these options was determined by patient preference, the degree of esophageal dysfunction, the severity of reflux disease, the length of BE, and presence of multifocal disease.⁵

Vagal-sparing esophagectomy removes the diseased esophagus but does not remove the lymph nodes; thus, it is applicable only for patients with HGD or intramucosal tumors. These patients have a low risk of lymph node metastases.⁶ In patients who elected to undergo endoscopic therapy for their disease, our preferred approach consisted of endoscopic resection for any nodules within the Barrett segment, and radiofrequency ablation for residual intestinal metaplasia, until BE was completely eradicated.⁵ Endoscopy was performed 8 weeks after endotherapy. If any intestinal metaplasia was still present, the patient underwent prompt reablation or additional endoscopic resection. This pattern was repeated until all the intestinal metaplasia was eradicated. Once the patient was rendered free of intestinal metaplasia, surveillance endoscopies were done every 3 months for the first year, every 6 months for the second year, and annually thereafter. Any recurrence of intestinal metaplasia was treated with additional endoscopic ablation or resection.

Staging

Patients with HGD or intramucosal cancer proven by endoscopic resection did not undergo routine positron emission tomography, computed tomography, or endoscopic ultrasonography. Patients with submucosal or deeper tumors underwent routine endoscopic ultrasonography and computed tomography-positron emission tomography, with additional staging studies as indicated. Patients with evidence of stage N2 disease (3-6 involved nodes) were typically offered neoadjuvant therapy. After therapy completion, the patients underwent repeat staging studies and, in the absence of metastatic disease, were offered esophagectomy. Staging was reported according to the 7th edition of the Cancer Staging Manual by the American Joint Committee on Cancer.⁷

Statistical Analysis

Comparisons of proportions were performed using the Fisher exact test or chi-square analysis. Survival estimates were calculated according to the Kaplan-Meier method and compared using log-rank analysis.

RESULTS

A total of 224 patients were treated with endotherapy or esophagectomy for HGD or invasive esophageal

adenocarcinoma during the 6-year study period: 36 in the surveillance group and 188 in the prevalence group. The characteristics, treatment, and tumor stage of patients in the 2 groups are listed in Table 1. No significant differences were found in age or gender; however, the patients in the surveillance group had a significantly greater prevalence and longer duration of reflux symptoms. All but 7 of the 36 surveillance patients had undergone surveillance elsewhere and were referred to our center for evidence of disease progression. The surveillance interval ranged from 6 months to 4 years, and the median number of endoscopies before the one showing progression was 3 in the surveillance group. In contrast, most patients in the prevalence group had not previously undergone endoscopy. Significantly more patients had HGD or intramucosal adenocarcinoma in the surveillance group (64%) compared with the prevalence group (26%). More than two thirds of the patients in the surveillance group first received endoscopic therapy compared with only 17% in the prevalent group. Also, 44% of the surveillance group had successful endotherapy and kept their esophagus compared with 12% in the prevalence group.

Esophagectomy was performed in 20 of the 36 patients (56%) in the surveillance group. Of these 20 patients, 9 first received endotherapy and subsequently underwent esophagectomy because the lesion was found to be invasive into the submucosa on endoscopic resection (2 patients), multifocal intramucosal cancer was present (5 patients), or patient preference or failed attempts at endotherapy (2 patients). Almost one half of the esophagectomies could be done with a vagal-sparing technique, given the superficial disease in these patients. In contrast, in the prevalence group, 166 of the 188 patients (88%) underwent esophagectomy, and only 7% were eligible for a vagal-sparing approach. In the prevalence group, 10 patients were initially treated with endotherapy but underwent esophagectomy for invasion into the submucosa on endoscopic resection (5 patients), multifocal intramucosal cancer (1 patient), and patient preference or failed attempts at endotherapy (4 patients). No patient in the surveillance group received neoadjuvant therapy, and 80% of those who underwent esophagectomy had node-negative disease. In contrast, 32% of patients in the prevalence group received neoadjuvant therapy, and, after esophagectomy, 49% had involved lymph nodes, with almost one fourth having 7 or more lymph node metastases (N3 disease).

The 90-day mortality rate in the surveillance group was 0% compared with 1% in the prevalence group. The median, disease-free, and overall survival were significantly better in the surveillance group (Figure 1). In the subgroup of patients with HGD or intramucosal (T1a) lesions, no cancer-related deaths had occurred in either group at a median follow-up of 22 months.

TABLE 1. Patient characteristics, tumor stage, and treatment

Characteristic	Surveillance group (n = 36)	Prevalence group (n = 188)	P value
Age (y)			
Median	70	69	NS
IQR	64-81	60-77	
Gender (n)			NS
Male	33	166	
Female	3	22	
Lifetime prevalence of GERD symptoms	36/36 (100%)	119 (63%)	<.0001
Duration of reflux symptoms (y)			<.0001
Median	30	5	
IQR	20-40	0-20	
Indication for EGD	NA		
Dysphagia		91 (48%)	
Anemia/GI bleed		27 (14%)	
Pain (abdomen, chest)		17 (9%)	
Other		53 (28%)	
Endoscopy before HGD or EA diagnosis (n)			NS
Median	3	0	
IQR	2-5		
Treatment			
Endotherapy (resection ± ablation)	25 (69%)	32 (17%)	<.0001
Endotherapy only	16/36 (44%)	22/188 (11%)	<.0001
Initial endotherapy, subsequent	9/36 (25%)	10/188 (5%)	.0005
Esophagectomy			<.0001
Esophagectomy as initial therapy	11 (31%)	156 (83%)	<.0001
Esophagectomy type			<.0001
Vagal-sparing	9 (45%)	12 (7%)	
All other types	11 (55%)	154 (93%)	
Neoadjuvant therapy	0	60 (32%)	<.0001
Follow-up (mo)			.04
Median	35	24	
IQR	19-46	13-41	
Pathologic T stage			<.0001
ypT0	NA	12 (6%)	
HGD	5 (14%)	8 (4%)	
T1a	18 (50%)	41 (22%)	
T1b	11 (31%)	15 (8%)	
T2	2 (6%)	26 (14%)	
T3	0	86 (46%)	
Esophagectomy patients only	20	166	
Pathologic N stage			.04
N0	16 (80%)	84 (51%)	
N1 (1-2 positive nodes)	3 (15%)	22 (13%)	
N2 (3-6 positive nodes)	1 (5%)	23 (14%)	
N3 (≥7 positive nodes)	0	37 (22%)	
Overall survival (mo)	59	55	.01
3-Year disease-free survival*	15/17 (88%)	47/105 (45%)	.0011

NS, Not significant; GERD, gastroesophageal reflux disease; IQR, interquartile range; EGD, esophagogastroduodenoscopy; NA, not applicable; GI, gastrointestinal; HGD, high-grade dysplasia; EA, esophageal adenocarcinoma. *Patients who completed at least 3 years of follow-up.

DISCUSSION

The incidence of BE is increasing and has been estimated to be present in 5.6% of the general population in the United States.^{8,9} BE is the only known precursor lesion for esophageal adenocarcinoma, the fastest increasing cancer in America.¹⁰ When BE progresses to cancer, it often does so in an orderly fashion, starting with nondysplastic

BE and progressing to low-grade dysplasia, HGD, and, finally, invasive adenocarcinoma. The recommendation for surveillance endoscopy for patients with BE is predicated on the concept that some patients with BE will develop disease progression and the identification of progression at a treatable or curable stage should improve survival. No randomized controlled trials have been

FIGURE 1. Kaplan-Meier curve showing overall survival in surveillance and prevalence groups.

published to support this concept, but several retrospective series have shown that compared with patients who present with prevalent or nonsurveillance-detected cancer, those who have their cancer identified within a surveillance program have earlier stage tumors and better survival.¹¹⁻¹³ The treatment of progression in these previous studies was esophagectomy. In the present study, we confirmed the finding that surveillance patients had earlier stage tumors and improved survival compared with patients who presented with prevalent cancer. HGD or intramucosal cancer was the final pathologic stage in 64% of patients in the surveillance group compared with 26% in the prevalent group. These early-stage lesions are nearly always curable, and in the present series, no patient died of cancer after treatment for HGD or intramucosal cancer. These are also the lesions amenable to endoscopic therapy, and the patients in the surveillance group were significantly more likely to receive endoscopic resection and/or ablation and to keep their esophagus than were patients in the prevalence group. In the later years of the study, the frequency and success of endoscopic therapy increased as we became more comfortable with extended endoscopic resections using the band technique and had better devices for ablation of residual BE.

Most patients in the surveillance group (29/36, 81%) were referred to us once progression to HGD or invasive adenocarcinoma was identified. In these 29 patients, the surveillance interval was as long as 4 years and 45% had tumors invasive into the submucosa or deeper whereas and 55% had lymph node metastases. Of this group, 14% have died of cancer. In contrast, 7 patients developed progression during surveillance at our institution. Of these, 4 had intramucosal adenocarcinoma and 3 had HGD. None of these 7 patients has died of cancer. Our policy has been annual endoscopic surveillance for nondysplastic BE; thus, all 7 of these patients were found with early-stage, curable disease. Although our surveillance group was too small to correlate tumor stage and survival with the surveillance interval, it is logical that a shorter interval will maximize the detection of earlier stage lesions and the potential for cure.

The findings in our study have relevance to the ongoing controversy regarding surveillance endoscopy for patients with BE.¹⁴⁻¹⁶ The arguments against surveillance have focused on the infrequency of disease progression, the inaccuracy of the histologic diagnosis of dysplasia, that most patients with adenocarcinoma present with prevalent disease with no previous diagnosis of BE, the morbidity and mortality of esophagectomy to treat disease progression, and the cost of surveillance with repeated endoscopy and biopsy.¹⁷ Given the cost and complexity of clinical trials to evaluate surveillance for BE, a number of studies have used a mathematical Markov model to explore hypothetical cohorts of patients with BE in an attempt to determine the cost-effectiveness of BE surveillance compared with other accepted practices, such as mammography for breast cancer and screening for colorectal cancer and organ transplantation. In 1999, Provenzale and colleagues¹⁸ concluded that surveillance every 5 years was the only viable strategy to provide an incremental cost-effectiveness ratio comparable with other accepted practices. In their model, the risk of progression to cancer was 0.4% annually, treatment of progression was esophagectomy, and the mortality with esophagectomy was 9.5%.¹⁸ Another study using the same Markov model, but with different values for some of the variables, concluded that biannual surveillance yielded an incremental cost-effectiveness ratio of \$16,965 per quality-adjusted life-year. This was more than screening for colorectal cancer (\$11,000) but less than erythropoietin therapy for anemia in dialysis patients (\$180,000). In that analysis, the risk of progression to cancer was 0.5%, treatment of progression was esophagectomy, and mortality with esophagectomy was 3.5%.¹⁹

These Markov models are very sensitive to the variables used for the analysis, including the rate of progression of BE to cancer. Recently, 2 studies were published that indicated that the rate of progression to cancer with BE was lower than the previously accepted rate of 0.5% annually.^{1,2} The first of these studies, a population-based study from Northern Ireland, found that the rate of progression to cancer was 0.16% annually.¹ The second study used a pathology registry that encompassed the entire population of Denmark and reported a rate of progression of 0.12% annually.² One problem in the study from Northern Ireland was the inclusion of patients with a columnar-lined esophagus without intestinal metaplasia. Although debated, most evidence has suggested that intestinal metaplasia is the hallmark of a mucosa at risk of progression to cancer.^{20,21} When the authors of the study from Northern Ireland restricted their analysis to those with intestinal metaplasia, the rate of progression to cancer increased to 0.27%, and when progression to HGD was included, the rate was 0.38% annually.¹ The study from Denmark included only patients with intestinal metaplasia; however, cancer at the gastroesophageal junction was not included.²

The length of BE was unknown in that study, but it is likely that many, if not most, patients had short segments.² Thus, exclusion of gastroesophageal junction cancer almost certainly led to a significant underappreciation of the true risk of progression.² Furthermore, both studies excluded all patients who developed cancer within the first year of the diagnosis of BE. The inclusion of these patients would have significantly increased the risk of progression (up to 0.29% in the Denmark study). Any discussion about surveillance must include these patients because, if they were not surveyed, they would have presented with prevalent cancer at some point after their diagnosis of BE.

Although the incidence of progression to cancer is one of the key variables in a Markov model of BE surveillance, other important variables include the type and cost of treatment for patients with progression and the morbidity and mortality associated with the treatment. All the published Markov analyses for BE surveillance used esophagectomy as the treatment for progression. In the decade since these studies were published, much has changed in the therapy for BE with progression during surveillance. One of the most significant changes has been the introduction of endoscopic therapy for HGD and intramucosal adenocarcinoma. In the present study, we have shown for the first time that patients found to have progression within a surveillance program are significantly more likely to be able to be treated with endoscopic resection and ablation than patients who present with prevalent cancer. Thus, nearly one half of the surveillance patients kept their esophagus. We have previously shown that although survival is similar, the morbidity with endoscopic therapy is significantly less than that with esophagectomy.³ Furthermore, survival is excellent with endotherapy or esophagectomy for early-stage disease. None of the patients treated for HGD or intramucosal adenocarcinoma in the present series died of cancer. Also, long-term cure with esophagectomy or endotherapy for patients with intramucosal adenocarcinoma has been shown in other series.^{3,22,23} Cure with resection alone in these patients refutes previous arguments that lead time bias is the only reason patients undergoing surveillance appear to have improved survival compared with nonsurveyed patients and that esophageal adenocarcinoma is a systemic disease at diagnosis.¹⁵

In the decade since the publication of these Markov models, esophagectomy has also changed and improved. Although mortality rates of 9.5% and 3.5% were used in the cited studies,^{1,2} no 90-day mortality after esophagectomy occurred in patients with progression during surveillance in the present study, and it was only 1% for patients with prevalent cancer. In those patients with only HGD or intramucosal adenocarcinoma, no mortality occurred after esophagectomy in either group, similar to other reports of patients with these early lesions.^{24,25} In the present series, 19 patients underwent esophagectomy (10% of the

esophagectomies) as a minimally invasive procedure. Benefits, such as reduced morbidity, shorter hospital stay, and faster recovery, could be present for these patients.^{26,27} Furthermore, almost one half of the esophagectomies in the surveillance group used a vagal-sparing technique. Vagal-sparing esophagectomy is applicable only for patients with HGD or intramucosal tumors, with a minimal risk of lymph node metastases, and is associated with reduced short- and long-term complications, including perioperative infections and postvagotomy dumping and diarrhea.²² The advantage of vagal-sparing esophagectomy over endoscopic therapy is that it is typically a “one-shot” treatment, without the need for repeat procedures, and eliminates the need for continued surveillance because of the risk of persistent or recurrent local disease in the esophagus.²⁸

In the present study, we also showed that patients with prevalent cancer were significantly more likely to be treated with neoadjuvant therapy, to have lymph node metastases, and to die of cancer. Given all these factors, it is inappropriate to assume that Markov models of surveillance, if repeated, would show worse cost-effectiveness than before solely because of the recently published lower estimates of the progression rates for BE. New studies need to include the cost of chemotherapy and radiotherapy, the cost of endotherapy versus esophagectomy, and the improved modern outcomes with these therapies in the Markov model. In addition, new modalities for surveillance and new methods to detect dysplasia, including technology such as optical coherence tomography, might make surveillance less costly and more reliable. Thus, the debate over surveillance for patients with BE is far from settled, and conclusions such as those in the recent study from Denmark that “the risk of esophageal adenocarcinoma among patients with Barrett’s is so minor that in the absence of dysplasia, routine surveillance of such patients is of doubtful value” are premature and unfounded.²

The issue of screening for BE is even more controversial than that of surveillance for known BE. Although 16% of the patients treated during our 6-year study period had surveillance-detected lesions, the unfortunate reality is that 84% presented with prevalent disease and no previous diagnosis of BE. Most had never had an endoscopy. This reflects the often-prompt institution of proton pump inhibitors by primary care physicians and gastroenterologists, without any additional evaluation beyond symptom assessment. However, it also reflects that many patients who present with a prevalent cancer never had significant reflux symptoms. This is a major issue in regard to screening. If screening endoscopy were recommended only for white men with long-standing heartburn or regurgitation symptoms, it would miss a large portion of the at-risk population. In our study, that was a small group among those with prevalent cancer. Thus, to be effective, screening likely would

need to be a general recommendation, perhaps at the age of 50 years, at the same time as a screening colonoscopy. Another issue, in regard to screening, is that 6 patients with prevalent cancer had undergone previous endoscopy within 5 years of the one that showed HGD or invasive adenocarcinoma. Disturbingly, in 3 patients, the previous endoscopy was within 1 year of the diagnosis. Typically, either erosive esophagitis or a normal esophagus was seen, but no biopsies were done. All these endoscopies were performed at outside facilities and reinforce the importance of routine biopsies at the gastroesophageal junction and systematically within a columnar-lined esophagus, with particular focus on any lesions or nodules in the columnar mucosa. Perhaps new, nonendoscopic screening techniques, such as the cytosponge, developed by Lao-Sirieix and Fitzgerald,²⁹ that uses immunohistochemical biomarkers rather than cytology to identify BE within a specimen, will allow cost-effective and reliable screening within a broad population.

Our study had important limitations. It was a single-institutional experience, and the numbers of patients, particularly in the surveillance group, were relatively small. However, as a regional referral center for gastroesophageal reflux disease, BE, and adenocarcinoma, we have no reason to believe that any type of referral bias existed, either for the surveillance-detected or prevalent lesions. Because most of the patients in each group were referred with their disease, we had to arbitrarily define what constituted surveillance for the purposes of our study. We decided that the fairest definition for a surveillance patient would be a patient who was aware they had BE and had had at least one endoscopy showing BE, with at most low-grade dysplasia, a minimum of 6 months before the endoscopy showing HGD or invasive adenocarcinoma. It would have been ideal if most of the patients with progression had come from within our own cohort of patients with BE undergoing standardized, yearly endoscopic surveillance. However, most of our patients with BE undergoing surveillance had had an antireflux procedure, and it is possible that the risk of progression in these patients is reduced. The effect of an antireflux procedure on the risk of progression in BE remains controversial and was outside the scope of the present study.^{30,31} Additional limitations include that we did not know the denominator of all patients with BE and/or adenocarcinoma evaluated at our center from which to give a frame of reference for the surveillance and prevalence groups included in the present study. Furthermore, there likely were patients with prevalent cancer who developed progression during neoadjuvant therapy and never underwent esophagectomy. These patients were not included in the present analysis, and neither were patients who presented with prevalent cancer and metastatic disease and underwent definitive chemoradiotherapy or palliative interventions. The inclusion of these patients undoubtedly would have further separated the surveillance and prevalence groups.

Despite these limitations, clear differences were seen between the groups and should encourage additional evaluation of the role of surveillance endoscopy and, perhaps, screening for BE.

CONCLUSIONS

Most patients with esophageal adenocarcinoma presented with prevalent disease with no previous diagnosis of BE. The majority of these patients had locally advanced disease and required esophagectomy, often with the addition of neoadjuvant chemoradiotherapy, in an attempt to cure the disease. In contrast, patients with disease progression within a BE surveillance program had earlier stage tumors, and most were treated with endoscopic resection and/or ablation. Significantly fewer patients in the surveillance group required esophagectomy, and the survival in this group was significantly better than that of patients with prevalent disease. These findings should encourage continued surveillance in patients with BE and perhaps consideration of cost-effective mechanisms to screen at-risk populations for the presence of BE.

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