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Esophagus (PG Iyer, Section Editor)

Predictors of Progression in Barrett's Esophagus

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Abstract

Purpose of review To review recently published data on factors that predict the risk of progression of Barrett's esophagus (BE) to high grade dysplasia (HGD) or esophageal adenocarcinoma (EAC).
Recent findings Computer models have been developed that could help predict the risk of progression with greater accuracy. The progression of BE score (PIB) is one such model based on clinical and endoscopic features, while a second uses automated image analysis of formalin-fixed and paraffin-embedded tissues looking for morphologic features and immunostaining patterns for molecular markers. Panels of genes such as those regulated by Myc and hypermethylated genes have been recently described.
Summary EAC remains a cancer with a poor 5-year survival of less than 20%. Screening for BE, the only known precursor of EAC is recommended only in high-risk individuals. Clinical, endoscopic, and molecular predictors of progression have been identified but require validation. These tools could in turn help focus screening and surveillance efforts to reduce mortality from EAC.

Introduction

The incidence and mortality of esophageal adenocarcinoma (EAC) in the USA have been steadily rising since the early 1970s. The 5-year overall survival rate for patients with EAC remains poor, at < 20%, and median survival after diagnosis is only 11 months. Barrett's esophagus (BE) is the only known precursor to EAC and can be detected endoscopically. Screening and surveillance to detect BE and dysplasia/EAC are hence recommended to enable prevention (by endoscopic treatment of dysplasia) and/or treatment of early stage EAC

[1]. Endoscopic surveillance is however only modestly effective likely due to a variety of reasons [2]. Compliance with endoscopic surveillance guidelines is poor, dysplasia distribution in BE mucosa is patchy and often subtle, leading to missed dysplasia [3]. Additionally, interobserver agreement among pathologists for the diagnosis of dysplasia (especially low-grade dysplasia) is moderate to poor. These limitations likely negatively impact the effectiveness of surveillance as currently practiced.

The degree of dysplasia on biopsy specimens obtained during upper endoscopy (EGD) is currently the only method utilized to predict progression to EAC and thereby determine surveillance intervals. Currently, progression (i.e., development of HGD or EAC) is defined as the detection of HGD or EAC more than 12 months after the initial diagnosis of BE. Population studies show that most patients with BE do not have dysplasia (80%) and the absolute risk of progression in non-dysplastic BE (NDBE) is low at 0.33% each year [4, 5]. Endoscopic surveillance in those with NDBE is recommended every 3 to 5 years, and biopsies are recommended every 2 cm in a four-quadrant fashion (Seattle protocol). Modeling studies have found surveillance in those with NDBE to not be cost-effective [6].

Hence, there is a strong clinical need to define predictors of progression in BE, in order to risk stratify patients into low- and high-risk categories, such that their surveillance and management can be tailored to this classification. In this review, we aim to comprehensively review and summarize the literature on predictors of progression in BE.

Patient characteristics that predict progression

Patient factors reported to increase risk of progression in BE patients include male gender and advancing age [7]. In a recent systematic review and meta-analysis (SRM) of cohort studies, significant associations between risk of progression and increasing age (OR 1.03, 95% CI 1.01–1.05, $I^2 = 45$) as well as male gender (OR 2.16, 95% CI 1.84–2.53, $I^2 = 0$) were reported.

While obesity is an established risk factor for BE and EAC [7], data on its direct impact on progression in those with known BE are more limited. In a large population-based cohort of BE patients, being overweight (BMI 25–29.9) conferred an increased risk of progression to EAC (OR 1.64). However, there was no effect of higher grades of obesity on progression [8]. Similarly, in another SRM, obesity as measured by BMI did not associate with the risk of progression [9••]. However, in a prospective cohort study, increased levels of serum Leptin and insulin resistance (which are associated with central obesity) were associated with progression, particularly in men [10]. Central obesity or visceral abdominal fat may be more closely associated with esophageal carcinogenesis than BMI which is a measure of overall adiposity [11].

Smoking is also a well-established risk factor for BE [12]. In a SRM of cohort studies, smoking was associated with an increased risk for progression of almost 50% [9••]. In this SRM, when analysis was restricted to the five studies that reported multivariate analyses adjusted for age and sex, smoking remained predictive of progression. However in the two studies adjusting for age, sex, and BE characteristics (baseline dysplasia and/or BE length), smoking was not predictive of progression. Additional studies have also consistently shown that smoking is a risk factor for EAC (OR 1.96, 95% CI 1.64–1.34, $I^2 = 24$) [13] along with a dose response effect. Hence, smoking may be one of the few modifiable risk factors influencing BE progression.

Medications such as aspirin/nonsteroidal anti-inflammatory drugs (NSAIDs), statins, and proton pump inhibitors (PPIs) have been reported to protect against progression of BE. In a SRM, the use of proton pump inhibitors (PPIs) and statins was associated with decreased odds of progression (ORs 0.55 and 0.48, respectively). While there is some evidence on the role of metformin, the chemoprevention of other malignancies, evidence for its role in preventing EAC in BE, appears to be limited [8, 14, 15].

Alcohol use does not appear to affect the risk of progression [8]. Another meta-analysis including 882 cases of BE progression in 6867 patients also found that alcohol consumption was not associated with the risk of neoplastic progression in BE [15, 16].

Endoscopic predictors of progression

BE segment length has been fairly consistently associated with increased risk of progression (Table 1). In an SRM data from 10 studies, the risk of progression increased by 25% (HR 1.25, 1.16–1.36) for every 1-cm increase in the length of BE (heterogeneity was moderate, $I^2 = 47$). This association remained significant even when the analysis was limited to six studies adjusting for age and sex and the three studies adjusting for baseline dysplasia as well. Indeed, in a recent multicenter cohort study, the annual risk of progression to HGD/EAC in those with long segment BE (≥ 3 cm) of 0.91% was substantially higher than that with short segment BE (1–3 cm) of 0.29% [17].

Endoscopic evidence of nodularity may reflect the presence of prevalent dysplasia or EAC and predict progression to HGD/EAC. In a retrospective cohort study, patients with NDBE and low-grade dysplasia (LGD) progressed to HGD/EAC at a rate of 0.97% per year (0.59% per person years in NDBE and 1.23% per person years in LGD). Nodularity on endoscopy predicted a 5-fold higher risk of progression (HR 4.98; 95% CI 1.80–11.7). In another cohort study of patients with LGD, nodularity increased the risk of progression more than 6-fold: HR 6.4 (0.98–24.3) [1, 18–20].

Dysplasia as a predictor of progression

NDBE

The rate of progression of NDBE to HGD or EAC is low. In a large Danish cohort, the annual risk of progression from NDBE to EAC was 0.1%. However, this was a pathology database study, with no information provided on the length of the BE segment, raising the possibility of misclassification bias (patients with intestinal metaplasia of the cardia being classified as BE). A somewhat similar rate of 0.17% was also observed among patients with NDBE in Northern Ireland although the latter included tumors arising in the gastric cardia in their calculation. A more comprehensive SRM reported that the annual risk of progression in NDBE is 0.33% [21]. In a retrospective cohort study of 1400 participants, the persistence of NDBE over consecutive endoscopies was associated with progressively decreasing odds of progression to EAC, though this has been refuted in other reports [4, 22].

Table 1. Models to predict progression in BE

Corresponding author	Type of predictors	Predictors	Technique	Outcome	Categories of risk progression	Accuracy of model
Sharma, P	Clinical features plus degree of dysplasia	Gender, cigarette smoking, length of BE, confirmed LGD	Assign points to each predictor and add up the points to calculate risk score	Annual risk of progression to HGD/EAC	Low risk (0.13%) Intermediate risk (0.73%) High risk (2.1%)	
Critchley-Thorne R.J.	Tissue morphology and biomarker	p16INK4a, AMACR, p53, HER2, K20, CD68 COX-2, HIF-1a, CD45RO	Automated analysis of FFPE slides for 15 morphologic features and IF pattern followed by calculation of risk scores	Progression from ND, IND or LGD to HGD or EAC within 12 months	Low risk (OR 1-reference) Intermediate risk (OR 7.7) High risk (OR 46)	AUROC progressors vs. non-progressors: 0.89

Indefinite for dysplasia

Indefinite for dysplasia is referred to "epithelial abnormalities insufficient to diagnose dysplasia or epithelial abnormalities that are unclear due to inflammation or sampling". The natural history of IND is still being elucidated. In a retrospective cohort study, 66 patients without prevalent dysplasia underwent surveillance endoscopy more than 1 year after the diagnosis of IND. Two (3%) developed HGD 16.5 and 28 months after the initial diagnosis of IND. Patients with incident dysplasia had a longer Barrett's segment and were more likely to report a history of smoking. Another retrospective study found that nearly 13% of patients with IND had prevalent dysplasia (seven LGD, two HGD) or EAC (two). Further, 17 of 82 patients (21%) progressed to dysplasia (82% LGD, 18% HGD) and two (0.2%) developed EAC. The incidence of advanced neoplasia (HGD/EAC) was 1.2 cases per 100 patient-years, which approximates that of LGD. Multi-focal IND and longer length of BE on the index biopsy predicted progression to advanced neoplasia [23]. Another retrospective cohort study from the Netherlands reported that the rate of progression from IND to HGD/EAC was 1.4 per 100 person years [24]. Hence, the preponderance of data seems to suggest that the risk of progression in IND may be comparable to that of BE-LGD.

LGD

The rate of progression of LGD to HGD or EAC varies based on the agreement between pathologists. In a SRM, the pooled annual incidence of EAC and EAC/HGD in patients with LGD was 0.54% and 1.73%, respectively. Stratifying the studies by proportion of LGD diagnosed in each study, denominator being total number of BE cases, less than or more than 15%), the annual incidence of EAC was 0.76% for a LGD/BE ratio less than 0.15 and 0.32% if the ratio was more than 0.15: suggestive of a low threshold for an LGD diagnosis. Substantial heterogeneity was observed in the overall analysis [5]. A key limitation of using LGD as a predictor of progression is the inter-observer variation among pathologists in diagnosing the presence of and grade of dysplasia. Studies where the proportion of LGD is high are expected to have a lower incidence of EAC given the over diagnosis of LGD. Conversely, the studies where proportion of LGD is low are expected to have a higher incidence of EAC because of more stringent diagnosis of LGD [5]. Additionally, the correlation between community pathologists and expert GI pathologists in making a diagnosis of LGD is poor, with most LGD diagnoses downgraded to NDBE on GI pathology review. In these downgraded patients, the risk of progression approximates that of NDBE patients (0.49%), while those with confirmed LGD, the rates of progression are substantially higher (13.4%) [25]. Hence, it is recommended that the diagnosis of LGD be confirmed by another pathologist with expertise in gastrointestinal pathology. Several studies have shown that persistent LGD (LGD demonstrated on more than surveillance endoscopy), confirmation of LGD by multiple GI pathologists and nodularity predict higher rates of progression [18, 26]. More recent studies have

also demonstrated that LGD may be a marker for prevalent HGD or IMC, and hence detection of LGD should prompt careful endoscopic follow-up [27, 28].

Genetic predictors of BE progression

EAC is a cancer with high mutation burden approaching that of cancers associated with known carcinogens like lung cancer and melanoma. It is also a genetically heterogeneous cancer, in that there are only a handful of genes including tumor suppressors *TP53* and *SMAD4* that are mutated consistently across multiple cases. *p16* mutation occurs independent of progression, while *p53* mutation is mostly seen in HGD and EAC and the *SMAD4* mutation is seen in EAC. A field effect has also been described in BE epithelium: *p53* mutation is often seen in the non-dysplastic area adjacent to EAC, more commonly in progressors than in non-progressors (18% vs. 7%).

In addition to point mutations, copy number changes and gene gains or deletions have also been described in progressors (summarized in Table 2). In one study, while the copy number profile of non-progressors remained relatively stable over time, in progressors, there was a marked increase from 0% at baseline to nearly 100% within 48 months of diagnosis of EAC. A panel comprising *TP53* loss of heterozygosity (LOH), *CDKN21* LOH, and presence of tetraploidy increased the risk of progression by nearly 39-fold [29]. In a prospective study, p53 protein expression was assessed using immunohistochemistry (IHC) and loss of p53 gene locus by fluorescent in situ hybridization (FISH) in 116 patients with BE. p53 overexpression (defined as 4+ expression on a scale of 0–4) was more common in LGD than in HGD or EAC, while p53 overexpression and loss of p53 gene locus together were more common in LGD, HGD, and EAC (Fig. 1). On multivariable analysis, overexpression of p53 and loss of TP53 gene locus were independent predictors of progression to HGD/EAC (HR = 17, 95% CI 3.2–

Table 2. Individual genetic biomarkers of progression in BE

Marker	Type of change	Type of study	Relative risk for progression
P53	Increased p53 expression by IHC	Nested case control	11.7 (1.9–71.4)
		Retrospective	5.6 (3.1–10.3)
	Absent p53 staining		14 (5.3–37.2)
	Absent p53 staining plus confirmed LGD		33% compared to 15% for absent p53 alone
TP53 LOH, CDKN2A LOH, and tetraploidy		Retrospective analysis of prospectively collected samples	38.7 (10.8–138.5)
Abnormal DNA ploidy, expression of *Aspergillus oryzae* lectin	No LGD at baseline		3.3 (1.8–6.1)
	LGD at baseline		3.9 (2.4–6.4)

From [19]

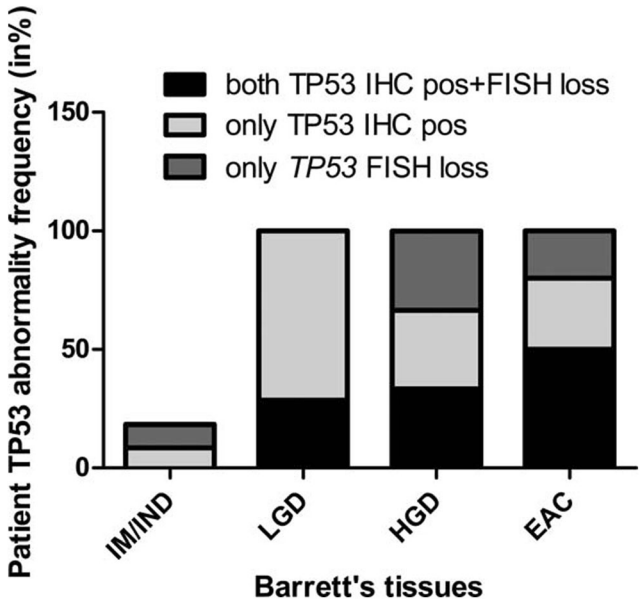

Fig. 1. Frequency distribution of p53 overexpression (by immunohistochemistry) and loss of TP53 gene locus by FISH by Barretts histologic categories [30].

96 and 7.3, 95% CI 1.3–41), respectively [30]. In a case-control study, 720 patients with BE were classified as cases if they developed HGD/EAC or as controls.

Overexpression of p53 was associated with increased risk of progression after adjusting for age, gender, length of BE, and esophagitis (adjusted RR 5.6, 3.1–10.3). Loss of p53 expression, although less common (5% vs 44% with p53 overexpression) was associated with an even higher risk of progression (RR 14, 5.3–37.2). Compared to normal p53 expression, aberrant p53 expression was associated with higher risk of progression in both NDBE (OR 4.5, 2.0–9.0) and LGD (11.2, 5.7–22.0) [31]. Finally, in a SRM, aberrant p53 expression was associated with increased risk of progression to EAC (OR 7.04, 3.68–13.46, $I^2 = 56\%$), remaining significant for both non-dysplastic BE (OR 6.12, 2.99–12.52) and LGD (OR 8.64, 3.62–20.62) (Fig. 2) [34].

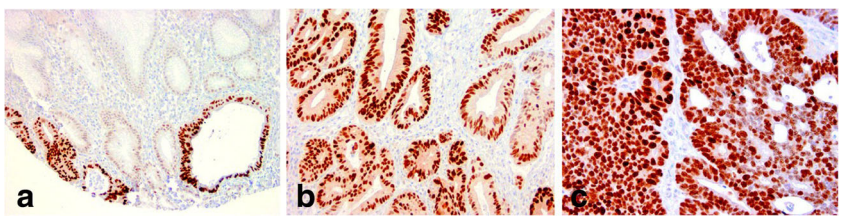

Fig. 2. p53 expression can be increased or is sometimes absent in BE. Top panel: **a** Negative control (no primary antibody) (× 200). **b** Barrett's mucosa with low-grade dysplasia, entire sample negative for p53 (× 400). **c** Barrett's mucosa with low-grade dysplasia, positive for p53 (× 400). **d** Barrett's mucosa with high-grade dysplasia, positive for p53 (× 400) [32]. *Bottom panel*: p53 immunostaining in a tissue array made from resected esophageal specimens. p53 expression in an area of high-grade dysplasia with adjacent mucosa negative for p53. **b** High-grade dysplasia with p53-positive immunostaining. **c** EAC with positive p53 immunostaining. In this study, 11% of NDBE, 0% of LGD, 57% of HGD, and 100% of EAC were positive for p53 [33].

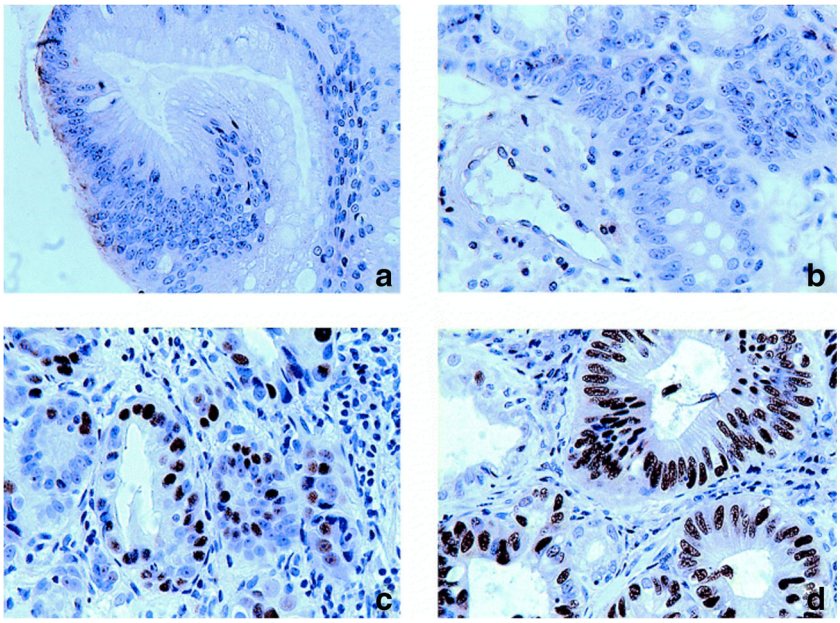

Fig. 2 continued.

A risk score that utilized LOH and microsatellite instability status of 10 specific loci also predicted progression to HGD. A combination of abnormal ploidy and expression of *Aspergillus oryzae* lectin (AOL) increased the odds of progression by 3–4-fold, with greater risk of progression in those with LGD [35]. A panel of four hypermethylated genes could stratify patients into low, intermediate, or high risk of progression with 94% sensitivity and 97% specificity, while another panel of eight genes distinguished progressors from non-progressors with an AUC of 0.84 and 0.83 at 2 and 4 years [36, 37].

A meta-analysis to identify genetic markers associated with susceptibility and progression of BE identified chromosomal instability as being significantly associated with increased odds of progression (Table 3). ORs for progression adjusted for length of BE and dysplasia ranged from 1.36–5.98. While LOH for

Table 3. Panel of biomarkers to predict risk of progression in BE

Marker	Number or genes	AUC
MYC-regulated genes	90	0.87 (0.82–0.93) to distinguish dysplastic from non-dysplastic BE 64% of LGD correctly at higher risk of progression correctly identified
Hypermethylated genes	4 (SLC22A18, PIGR, GJA12, RIN2)	Stratified patients into low, intermediate, high risk of progression with 94% sensitivity and 97% specificity
	8 genes (p16, RUNX3, HPP1, NELL1, TAC1, SST, AKAP12, CDH13)	AUC for BE progression 0.84 at 2 years and 0.83 at 4 years

From [19]

TP53 and *p16* and presence of a mutant *p53* were associated with higher odds of progression (ORs 5.4, 2.4 and 1.27, respectively), their odds ratios were not adjusted for degree of dysplasia.

Another prospective study from the Netherlands followed patients with NDBE with serial endoscopic biopsy surveillance (every 2–3 years for NDBE and 6 months for dysplastic BE) and brush cytology for fluorescence in situ hybridization (FISH). Four hundred ninety-eight patients were followed for a cumulative 2277 patient-years. Twenty-two patients progressed: nine developed HGD and 13 EAC (rate of progression to HGD/EAC was 0.97% per patient year). Univariate analysis revealed that loss of *p16*, gain of *MYC*, and aneusomy detected by FISH (using centromeric probes for chromosomes 7 and 17) were the genetic markers significantly associated with progression in NDBE. Age and length of circumferential BE were the other factors associated with progression. Age and the number of abnormal FISH markers remained significant predictors of progression on multivariable analysis. A model comprising of age, length of circumferential BE, and the number of abnormal markers had a 99% negative predictive value—i.e., 99% of patients would be correctly classified as non-progressors. Its positive predictive value, however, was only 9%. Hence, the panel appeared to be more helpful in identifying a low-risk group than a high risk group [38].

Models to predict risk of progression

Some investigators have attempted to develop models to predict the risk of progression using multiple clinical and biomarker-related variables. Using data from 2697 patients from a multicenter cohort, a risk assessment score using only clinical variables was recently proposed to predict the risk of progression to HGD or EAC (Table 4). This score has four components, each given a specific score—male gender (9 points), cigarette smoking (ever smoker getting 5 points), and length of BE segment (1 point for every 1-cm increase in length, up to a maximum of 10 points) and confirmed LGD (11 points). The total score is the sum of these four variables. Patients are divided into three categories stratified by annual risk of progression—low risk (0–10 points, 0.13%/year), intermediate risk (11–19 points, 0.73%/year), and high risk (> 20 points, 2.1%/year). The study was limited by lack of histological confirmation of the presence and degree of neoplasia by expert pathologists. Risk factors such as age, BMI, and medications (e.g., aspirin, NSAIDs, statin, and PPIs) were not significant predictors of progression of BE in this model [39••]. This score needs to be externally validated.

A second proposed BE progression prediction model is based on the field effect of cancer—i.e., pre-neoplastic changes in morphology and gene expression that surround areas of HGD or EAC (Table 4). The premise of this model is that detection of these alterations before progression (e.g., at index endoscopy which shows either NDBE, IND, or LGD) could potentially guide closer surveillance in those predicated to be at higher risk of progression. Using a case (patients who had HGD/EAC on repeat endoscopy within 1 year, or had prior history of treatment for HGD/EAC downgraded to NDBE/IND/LGD and then

Table 4. Models to predict progression in BE

Corresponding author	Type of predictors	Predictors	Technique	Outcome	Categories of risk progression	Accuracy of model
Sharma, P	Clinical features plus degree of dysplasia	Gender, cigarette smoking, length of BE, confirmed LGD	Assign points to each predictor and add up the points to calculate risk score	Annual risk of progression to HGD/EAC	Low risk (0.13%) Intermediate risk (0.73%) High risk (2.1%)	
Critchley-Thorne R.J.	Tissue morphology and biomarker	p16INK4a, AMACR, p53, HER2, K20, CD68 COX-2, HIF-1a, CD45RO	Automated analysis of FFPE slides for 15 morphologic features and IF pattern followed by calculation of risk scores	Progression from ND, IND or LGD to HGD or EAC within 12 months	Low risk (OR 1-reference) Intermediate risk (OR 7.7) High risk (OR 46)	AUROC progressors vs. non-progressors: 0.89

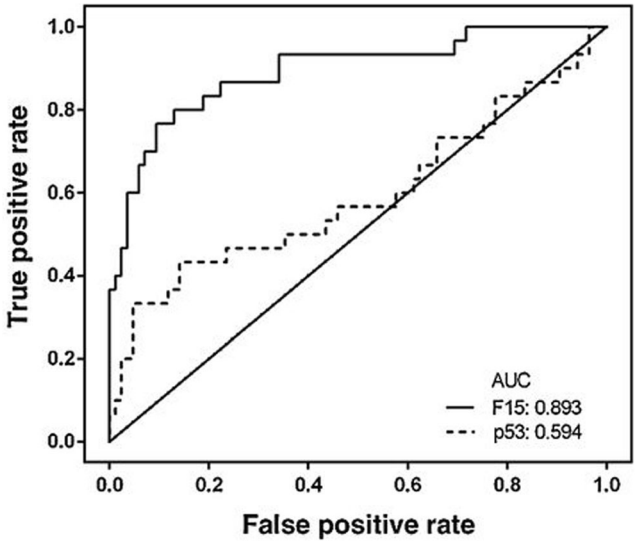

Fig. 3. An AUC curve compares the performance of a score using 15 features derived from automated image analysis to that of p53 in distinguishing progressors (HGD/EAC on repeat endoscopy within 1 year or previously treated HGD/EAC that returned to NDBE/LGD/IND followed by HGD/EAC on repeat endoscopy) from non-progressors (no HGD/EAC on follow-up).

had recurrent HGD/EAC) and control (i.e., patients who did not progress to HGD/EAC) study design and 15 variables including a combination of morphologic features and molecular marker expression, the authors created a model that could distinguish progressors from non-progressors with an area under the curve of 0.89 (Fig. 3). When progressors were subdivided into (a) those that were previously treated for HGD/EAC followed by regression to NDBE/IND/LGD or (b) those with no prior history of treatment for HGD/EAC, the model still predicted the development of HGD/EAC with good accuracy in either group (AUC 0.93 and 0.88, respectively). The advantage of this method was that it used automated image analysis of paraffin-embedded sections of mucosal biopsies thereby reducing inter-observer variability. Biomarker expression was assessed by immunofluorescence. The features extracted by the image analysis program were used to create a computer model which assigned a score from zero to 10. Based on the score, patients were divided into one of three categories—low, intermediate, or high risk for progression to HGD/EAC. Interestingly, the study found that in a patient with NDBE at one level and LGD at another level who progressed to HGD, the risk score was the same for the areas with NDBE and LGD, suggesting that the molecular changes due to the field effect do precede morphologic changes. One of the strengths of this model was that the diagnosis of BE and dysplasia was evaluated by three expert GI pathologists [40••].

Conclusions

Progression of BE to HGD or EAC is affected by patient demographics, lifestyle, medications, endoscopic features, and molecular markers. Recently, models have been described that help to stratify risk of progression better. Further studies are needed to validate these models and identify optimal strategies for

surveillance or therapy in patients at high risk of progression as well as determine their true negative predictive value.

Compliance with Ethical Standards

Conflict of Interest
Subhankar Chakraborty declares that he/she has no conflict of interest. Prasad Iyer reports grants from Exact Sciences, Pentax Medical, Intromedic, non-financial support from Medtronic, and is a consultant for Medtronic and CSA Medical.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Heading

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Nguyen T, Thrift AP, Yu X, Duan Z, El-Serag HB. The annual risk of esophageal adenocarcinoma does not decrease over time in patients with Barrett's esophagus. Am J Gastroenterol. 2017;112(7):1049–55. https://doi.org/10.1038/ajg.2017.18.
2. Codipilly DC, Chandar AK, Singh S, Wani S, Shaheen NJ, Inadomi JM, et al. The effect of endoscopic surveillance in patients with Barrett's esophagus: a systematic review and meta-analysis. Gastroenterology. 2018;154(8):2068–86 e5. https://doi.org/10.1053/j.gastro.2018.02.022.
3. Visrodia K, Singh S, Krishnamoorthi R, Ahlquist DA, Wang KK, Iyer PG, et al. Magnitude of missed esophageal adenocarcinoma after Barrett's esophagus diagnosis: a systematic review and meta-analysis. Gastroenterology. 2016;150(3):599–607 e7; quiz e14–5. https://doi.org/10.1053/j.gastro.2015.11.040.
4. Gaddam S, Singh M, Balasubramanian G, Thota P, Gupta N, Wani S, et al. Persistence of nondysplastic Barrett's esophagus identifies patients at lower risk for esophageal adenocarcinoma: results from a large multicenter cohort. Gastroenterology. 2013;145(3):548–53 e1. https://doi.org/10.1053/j.gastro.2013.05.040.
5. Singh S, Manickam P, Amin AV, Samala N, Schouten LJ, Iyer PG, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79(6):897–909 e4; quiz 83 e1, 83 e3. https://doi.org/10.1016/j.gie.2014.01.009.
6. Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. Ann Intern Med. 2003;138(3):176–86.
7. Singh S, Sharma AN, Murad MH, Buttar NS, El-Serag HB, Katzka DA, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399–412 e7. https://doi.org/10.1016/j.cgh.2013.05.009.
8. Krishnamoorthi R, Borah B, Heien H, Das A, Chak A, Iyer PG. Rates and predictors of progression to esophageal carcinoma in a large population-based Barrett's esophagus cohort. Gastrointest Endosc. 2016;84(1):40–6 e7. https://doi.org/10.1016/j.gie.2015.12.036S0016-.
9.•• Krishnamoorthi R, Singh S, Ragunathan K, Visrodia K, Wang KK, Katzka DA, et al. Factors associated with progression of Barrett's esophagus: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16(7):1046–55 e8. https://doi.org/10.1016/j.cgh.2017.11.044.

A recent systemic review and meta-analysis that found that age, male gender, smoking and increasing length of BE segment increase while use of PPIs and statins lower the risk of BE progression.

10. Duggan C, Onstad L, Hardikar S, Blount PL, Reid BJ, Vaughan TL. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. Clin Gastroenterol Hepatol. 2013;11(8):934–43. https://doi.org/10.1016/j.cgh.2013.02.017.
11. Di Caro S, Cheung WH, Fini L, Keane MG, Theis B, Haidry R, et al. Role of body composition and metabolic profile in Barrett's oesophagus and progression to cancer. Eur J Gastroenterol Hepatol. 2016;28(3):251–60. https://doi.org/10.1097/MEG.0000000000000536.
12. Andrici J, Cox MR, Eslick GD. Cigarette smoking and the risk of Barrett's esophagus: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2013;28(8):1258–73. https://doi.org/10.1111/jgh.12230.
13. Cook MB, Kamangar F, Whiteman DC, Freedman ND, Gammon MD, Bernstein L, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2010;102(17):1344–53. https://doi.org/10.1093/jnci/djq289.
14. Chak A, Buttar NS, Foster NR, Seisler DK, Marcon NE, Schoen R, et al. Metformin does not reduce markers of cell proliferation in esophageal tissues of patients with Barrett's esophagus. Clin Gastroenterol Hepatol. 2015;13(4):665–72 e1-4. https://doi.org/10.1016/j.cgh.2014.08.040.
15. Agrawal S, Patel P, Agrawal A, Makhijani N, Markert R, Deidrich W. Metformin use and the risk of esophageal cancer in Barrett esophagus. South Med J. 2014;107(12):774–9. https://doi.org/10.14423/SMJ.0000000000000212.
16. Lou Z, Xing H, Li D. Alcohol consumption and the neoplastic progression in Barrett's esophagus: a systematic review and meta-analysis. PLoS One. 2014;9(10):e105612. https://doi.org/10.1371/journal.pone.0105612.
17. Hamade N, Vennelaganti S, Parasa S, Vennalaganti P, Gaddam S, Spaander MCW, et al. Lower annual rate of progression of short-segment vs long-segment Barrett's esophagus to esophageal adenocarcinoma. Clin Gastroenterol Hepatol. 2018. https://doi.org/10.1016/j.cgh.2018.07.008.
18. Krishnamoorthi R, Lewis JT, Krishna M, Crews NJ, Johnson ML, Dierkhising RA, et al. Predictors of progression in Barrett's esophagus with low-grade dysplasia: results from a multicenter prospective BE registry. Am J Gastroenterol. 2017;112(6):867–73. https://doi.org/10.1038/ajg.2017.84.
19. Gregson EM, Bornschein J, Fitzgerald RC. Genetic progression of Barrett's oesophagus to oesophageal adenocarcinoma. Br J Cancer. 2016;115(4):403–10. https://doi.org/10.1038/bjc.2016.219.
20. Findlay JM, Middleton MR, Tomlinson I. Genetic biomarkers of Barrett's esophagus susceptibility and progression to dysplasia and cancer: a systematic review and meta-analysis. Dig Dis Sci. 2016;61(1):25–38. https://doi.org/10.1007/s10620-015-3884-5.
21. Desai TK, Samala N. The incidence of esophageal adenocarcinoma among patients with nondysplastic Barrett's esophagus has been overestimated. Clin Gastroenterol Hepatol. 2011;9(4):363–4; author reply 4-5. https://doi.org/10.1016/j.cgh.2010.11.009.
22. Krishnamoorthi R, Ramos GP, Crews N, Johnson M, Dierkhising R, Shi Q, et al. Persistence of nondysplastic Barrett's esophagus is not protective against progression to adenocarcinoma. Clin Gastroenterol Hepatol. 2017;15(6):950–2. https://doi.org/10.1016/j.cgh.2017.02.019.
23. Horvath B, Singh P, Xie H, Thota PN, Allende DS, Pai RK, et al. Risk for esophageal neoplasia in Barrett's esophagus patients with mucosal changes indefinite for dysplasia. J Gastroenterol Hepatol. 2015;30(2):262–7. https://doi.org/10.1111/jgh.12696.
24. Kestens C, Leenders M, Offerhaus GJ, van Baal JW, Siersema PD. Risk of neoplastic progression in Barrett's esophagus diagnosed as indefinite for dysplasia: a nationwide cohort study. Endoscopy. 2015;47(5):409–14. https://doi.org/10.1055/s-0034-1391091.
25. Curvers WL, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, et al. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. Am J Gastroenterol. 2010;105(7):1523–30. https://doi.org/10.1038/ajg.2010.171.
26. Whitson MJ, Falk GW. Predictors of progression to high-grade dysplasia or adenocarcinoma in Barrett's esophagus. Gastroenterol Clin N Am. 2015;44(2):299–315. https://doi.org/10.1016/j.gtc.2015.02.005.
27. Rubenstein JH, Waljee AK, Dwamena B, Bergman J, Vieth M, Wani S. Yield of higher-grade neoplasia in Barrett's esophagus with low-grade dysplasia is double in the first year following diagnosis. Clin Gastroenterol Hepatol. 2018;16(9):1529–30. https://doi.org/10.1016/j.cgh.2018.01.002.
28. Wani S, Qumseya B, Sultan S, Agrawal D, Chandrasekhara V, Harnke B, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. Gastrointest Endosc. 2018;87(4):907–31 e9. https://doi.org/10.1016/j.gie.2017.10.011.
29. Galipeau PC, Li X, Blount PL, Maley CC, Sanchez CA, Odze RD, et al. NSAIDs modulate CDKN2A, TP53, and DNA content risk for progression to esophageal adenocarcinoma. PLoS Med. 2007;4(2):e67. https://doi.org/10.1371/journal.pmed.0040067.
30. Davelaar AL, Calpe S, Lau L, Timmer MR, Visser M, Ten Kate FJ, et al. Aberrant TP53 detected by combining immunohistochemistry and DNA-FISH improves Barrett's esophagus progression prediction: a prospective follow-up study. Genes Chromosom Cancer. 2015;54(2):82–90. https://doi.org/10.1002/gcc.22220.

31. Kastelein F, Biermann K, Steyerberg EW, Verheij J, Kalisvaart M, Looijenga LH, et al. Aberrant p53 protein expression is associated with an increased risk of neoplastic progression in patients with Barrett's oesophagus. Gut. 2013;62(12):1676–83. https://doi.org/10.1136/gutjnl-2012-303594.
32. Weston AP, Banerjee SK, Sharma P, Tran TM, Richards R, Cherian R. p53 protein overexpression in low grade dysplasia (LGD) in Barrett's esophagus: immunohistochemical marker predictive of progression. Am J Gastroenterol. 2001;96(5):1355–62. https://doi.org/10.1111/j.1572-0241.2001.03851.x.
33. Keswani RN, Noffsinger A, Waxman I, Bissonnette M. Clinical use of p53 in Barrett's esophagus. Cancer Epidemiol Biomark Prev. 2006;15(7):1243–9. https://doi.org/10.1158/1055-9965.EPI-06-0010.
34. Janmaat VT, van Olphen SH, Biermann KE, Looijenga LHJ, Bruno MB, Spaander MCW. Use of immunohistochemical biomarkers as independent predictor of neoplastic progression in Barrett's oesophagus surveillance: a systematic review and meta-analysis. PLoS One. 2017;12(10):e0186305. https://doi.org/10.1371/journal.pone.0186305PONE-D-17-.
35. Bird-Lieberman EL, Neves AA, Lao-Sirieix P, O'Donovan M, Novelli M, Lovat LB, et al. Molecular imaging using fluorescent lectins permits rapid endoscopic identification of dysplasia in Barrett's esophagus. Nat Med. 2012;18(2):315–21. https://doi.org/10.1038/nm.2616.
36. Alvi MA, Liu X, O'Donovan M, Newton R, Wernisch L, Shannon NB, et al. DNA methylation as an adjunct to histopathology to detect prevalent, inconspicuous dysplasia and early-stage neoplasia in Barrett's esophagus. Clin Cancer Res. 2013;19(4):878–88. https://doi.org/10.1158/1078-0432.CCR-12-2880.
37. Jin Z, Cheng Y, Gu W, Zheng Y, Sato F, Mori Y, et al. A multicenter, double-blinded validation study of methylation biomarkers for progression prediction in Barrett's esophagus. Cancer Res. 2009;69(10):4112–5. https://doi.org/10.1158/0008-5472.CAN-09-0028.
38. Timmer MR, Martinez P, Lau CT, Westra WM, Calpe S, Rygiel AM, et al. Derivation of genetic biomarkers for cancer risk stratification in Barrett's oesophagus: a prospective cohort study. Gut. 2016;65(10):1602–10. https://doi.org/10.1136/gutjnl-2015-309642.
39.•• Parasa S, Vennalaganti S, Gaddam S, Vennalaganti P, Young P, Gupta N, et al. Development and validation of a model to determine risk of progression of Barrett's esophagus to neoplasia. Gastroenterology. 2018;154(5):1282–9 e2. https://doi.org/10.1053/j.gastro.2017.12.009.

This study describes a new score based on computer modeling based on clinical, endoscopic features and degree of dysplasia to predict progression of BE to HGD/EAC.

40.•• Critchley-Thorne RJ, Davison JM, Prichard JW, Reese LM, Zhang Y, Repa K, et al. A tissue systems pathology test detects abnormalities associated with prevalent high- grade dysplasia and esophageal cancer in Barrett's esophagus. Cancer Epidemiol Biomark Prev. 2017;26(2):240–8. https://doi.org/10.1158/1055-9965.EPI-16-0640.

This study describes a computer model using automated analysis of tissue morphology and staining for molecular markers to stratify risk of progression in BE.