Published in final edited form as:

Clin Gastroenterol Hepatol. 2018 September ; 16(9): 1529–1530. doi:10.1016/j.cgh.2018.01.002.

Yield of higher-grade neoplasia in Barrett's esophagus with low-grade dysplasia is double in the first year following diagnosis

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Keywords

Esophageal neoplasms; Barrett esophagus; precancerous conditions; meta-analysis; bias

INTRODUCTION

Barrett's esophagus (BE) is the only known precursor of esophageal adenocarcinoma (EAC). BE is believed to progress through dysplasia prior to developing EAC. Histologic evidence of dysplasia is the only widely used biomarker for predicting neoplastic progression. Management of BE with low grade dysplasia (LGD) is challenging due to poor inter-observer variability among pathologists for the diagnosis, and heterogeneous rates of neoplastic progression reported from various cohorts. In addition, endoscopists inexperienced in managing dysplasia might not recognize endoscopic lesions of early neoplasia, accentuating the propensity of sampling error in patients found to have LGD but actually harboring high grade dysplasia (HGD) or early cancer in other areas of the esophagus. We therefore hypothesized that the observed progression rate to HGD or cancer within the first year following diagnosis of BE with LGD would be greater than overall

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Specific author contributions: JHR: design, acquisition of data, interpretation of data, and drafting the manuscript; AW: analysis of data, interpretation of data, drafting the manuscript; BD: analysis of data, interpretation of data, critical revision of the manuscript; JB: design, interpretation of data, critical revision of the manuscript; MV: design, interpretation of data, critical revision of the manuscript; SW: design, acquisition of data, interpretation of data, and critical revision of the manuscript.

Conflicts of interest: SW is a consultant for Medtronic and Boston Scientific. The other authors have no relevant financial or personal conflicts of interest.

annual progression rate. If so, it would suggest that surveillance in the first year following diagnosis should be more frequent than subsequently.

METHODS

We conducted a systematic review in MEDLINE, EMBASE, and Cochrane Library from 1980 to January 2016 to identify publications that reported both the overall annual incidence of HGD or cancer in patients with BE LGD and also reported the progression within the first year following diagnosis of BE LGD. The search strategy in MEDLINE was ((Barrett Esophagus or barrett*) or (esophagus and (metaplasia or intestine metaplasia or (intestine* adj2 metaplasia))) and ((early diagnosis or precancerous conditions or (precancer or dysplasia) or (lgd or ((low grade adj3 dysplas*) or (no dysplas* pre?neoplas* or pre? cancer*))). Similar queries were performed in the other databases. Non-English studies and those that reported subjects in duplicate to another study were excluded.

The primary outcome was the median incidence rate ratio from a hierarchical Poisson meta-analysis which accounted for heterogeneity between studies and the correlation between the two rates within studies. In addition, meta-analyses estimated the rates of progression from LGD to either HGD or cancer during the first year, and annual rates of progression through the entire duration of follow-up, each using a random-effects model. Heterogeneity across the studies was estimated using the inconsistency index (I^2), where $< 25\%$ is considered low heterogeneity and $> 75\%$ high heterogeneity, and $p < 0.05$ indicates statistically significant heterogeneity. Analyses were performed in Stata v. 14 (StatCorp, College Station, TX).

RESULTS

The initial queries identified 1,492 articles. After initial review of titles and abstracts, 126 articles were obtained for review. Of those, 13 studies excluded cases that progressed within the first year and did not provide the number of such subjects. A total of 8 studies were eligible (including reporting such data) and were included in the meta-analyses (Table 1).¹⁻⁸

The weighted summary annual incidence of the entire follow-up period from LGD to either HGD or cancer was 4.6 per 100 patient-years (95% confidence interval [CI] = 2.0, 7.2) with moderate heterogeneity ($I^2 = 51\%$, $p=0.04$ for test of heterogeneity). The weighted summary first year rate of progression was 8.8 per 100 patients (95% CI = 3.7, 13.8) with high heterogeneity ($I^2 = 77\%$, $p < 0.01$). The median incident rate ratio for first year vs. overall progression rates was 2.34, indicating that, accounting for between study heterogeneity, the incidence in the first year was approximately twice the overall annual progression rate.

DISCUSSION

We conducted a systematic review and series of meta-analyses finding that the incidence of HGD or cancer within the first year following diagnosis of LGD is approximately twice the annual incidence throughout follow-up. Most guidelines have recommended shorter intervals in the first year following diagnosis of LGD than subsequently, but based on expert opinion rather than empiric evidence. Our results confirm that the opinions of the experts in these guidelines are justified.

It is biologically implausible that the greater earlier yield represents true progression, but rather likely reflects misclassification of HGD or cancer as LGD due to sampling error or pathologist interpretation. For understanding the natural history of true LGD, many studies have excluded early progressors with the intent of avoiding misclassification. But for the purposes of clinical management of newly diagnosed BE LGD, the provider does not have foreknowledge regarding any misclassification. Relying on studies that exclude early progressors therefore overlooks the potential for misclassification and the potential benefit of early repeat endoscopy to evaluate for missed lesions. We found that the summary estimated first year rate of progression from LGD to HGD or cancer was 8.8%, a rate that we find substantial enough to warrant more frequent surveillance than in subsequent years.

Acknowledgments

The authors thank Kellee Kaulback, HBA, MIST, Medical Information Specialist for assistance with drafting the search strategy.

Financial support: JHR was supported by VHA grant I01-CX000899, NIH grant U01CA199336, and NIH grant U54CA163059. SW was supported by the University of Colorado Department of Medicine OESP. The funding agencies had no role in the collection, analysis, or interpretation of data.

ABBREVIATIONS

BE	Barrett's esophagus
CI	confidence interval
EAC	esophageal adenocarcinoma
HGD	high grade dysplasia
I²	inconsistency index
LGD	low grade dysplasia

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Table 1

Summary of included studies

Author (reference)	Year of publication	Country	Number of BE	Number of LGD	Diagnosis confirmed by another pathologist	Mean duration of follow-up (months)	1 st year Incidence of HGD/Ca (95% CI) ^f	Overall Incidence of HGD/Ca (95% CI) ^f
Skacel ¹	2000	United States	a	25	Yes	26	29 (13, 53)	8 (2, 30)
Montgomery ²	2001	United States	138	26	Yes	24	27 (14, 46)	10 (3, 27)
Alcedo ³	2009	Spain	340	32	No	b 51	0 (0, 11)	0 (0, 11)
Gatenby ⁴	2009	United Kingdom	1329	146	c Unclear	48	6 (3, 11)	2 (1, 6)
Curvers ⁵	2010	Netherlands	1198	19	Yes	51	0 (0, 17)	13 (4, 35)
Duits ⁶	2015	Netherlands	a	79	Yes	d 39	11 (6, 20)	9 (5, 17)
Picardo ⁷	2015	Ireland	1033	73	Yes	b 50	13 (7, 23)	4 (1, 11)
Thota ⁸	2015	United States	2370	299 e	Most	d 63	5 (3, 8)	3 (1, 5)

BE: Barrett's esophagus

CI: confidence interval

HGD/Ca: high grade dysplasia or cancer

LGD: low grade dysplasia

^a Only reported data on LGD in the article.^b Duration of follow-up reported is for cohort of BE overall. No data available for LGD specifically.^c The study was multi-center with each center using their "experienced consultant pathologist," but it was not clear if more than one pathologist reviewed the slides.^d Follow-up reported is median rather than mean.^e Included BE indefinite for dysplasia in the cohort. Data not separately reported for LGD.^f Incidence is per 100 patient-years