CME

REVIEW

The Risk of Lymph-Node Metastases in Patients With High-Grade Dysplasia or Intramucosal Carcinoma in Barrett's Esophagus: A Systematic Review

Kerry B. Dunbar, MD[1] and Stuart Jon Spechler, MD[1]

OBJECTIVES: **Endoscopic eradication therapy is used to treat mucosal neoplasms in Barrett's esophagus, but cannot cure cancers that have metastasized to lymph nodes. The risk of such metastases has been proposed as a reason to consider esophagectomy rather than endoscopic therapy for esophageal mucosal neoplasia. The objective of our study was to determine the frequency of lymph-node metastases in patients with high-grade dysplasia (HGD) and intramucosal carcinoma in Barrett's esophagus.**

METHODS: **We performed a systematic review using the PRISMA guidelines to identify studies that included patients who had esophagectomy for HGD or intramucosal carcinoma in Barrett's esophagus, and that reported final pathology results after examination of esophagectomy specimens.**

RESULTS: **We identified 70 relevant reports that included 1,874 patients who had esophagectomy performed for HGD or intramucosal carcinoma in Barrett's esophagus. Lymph-node metastases were found in 26 patients (1.39%, 95% CI 0.86–1.92). No metastases were found in the 524 patients who had a final pathology diagnosis of HGD, whereas 26 (1.93%, 95% CI 1.19–2.66%) of the 1,350 patients with a final pathology diagnosis of intramucosal carcinoma had positive lymph nodes.**

CONCLUSIONS: **The risk of unexpected lymph-node metastases for patients with mucosal neoplasms in Barrett's esophagus is in the range of 1–2%. Esophagectomy has a mortality rate that often exceeds 2%, with substantial morbidity and no guarantee of curing metastatic disease. Therefore, the risk of lymph-node metastases alone does not warrant the choice of esophagectomy over endoscopic therapy for HGD and intramucosal carcinoma in Barrett's esophagus.**

Am J Gastroenterol 2012; 107:850–862; doi:10.1038/ajg.2012.78; published online 10 April 2012

INTRODUCTION

Barrett's esophagus is the precursor of esophageal adenocarcinoma, a lethal tumor whose frequency has increased at an alarming rate over the past several decades (1). Cancers in Barrett's esophagus are thought to evolve through a sequence of genetic and epigenetic alterations that endow cells with growth advantages and cause histological changes in the metaplastic epithelium that pathologists recognize as dysplasia (2). For patients with Barrett's esophagus, regular endoscopic surveillance is advised primarily to detect dysplasia, which is a potentially curable form of neoplasia. The management of low-grade dysplasia remains highly controversial, but most experts agree that high-grade dysplasia (HGD) in Barrett's esophagus poses a sufficient risk for malignancy that intervention is warranted (3). Traditionally, that intervention was esophagectomy. Recently, endoscopic eradication has become the preferred therapy for HGD. The American Gastroenterological Association's recent position statement on the management of Barrett's esophagus concluded that "Most patients with HGD (70–80%) can be successfully treated with endoscopic eradication therapy (4)."

Endoscopic eradication therapy can eliminate neoplasms that are confined to the esophageal mucosa, but cannot cure cancers that have successfully metastasized to lymph nodes. For patients with esophageal adenocarcinomas that involve the submucosa, the frequency of lymph-node metastases is at least 20% (5), and therefore, endoscopic eradication therapy generally is deemed

[1]Department of Medicine, VA North Texas Healthcare System, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA.
Correspondence: Kerry B. Dunbar, MD, Division of Gastroenterology and Hepatology (111B1), Dallas VA Medical Center, 4500 South Lancaster Road, Dallas, Texas 75216, USA. E-mail: kerry.dunbar@va.gov
Received 4 November 2011; accepted 1 March 2012

inadequate as a curative treatment. That is why endoscopic mucosal resection (EMR) is advised for T staging in patients who have Barrett's esophagus with dysplasia that is associated with visible mucosal irregularities (3,4). If EMR of such lesions reveals no submucosal invasion, then endoscopic eradication therapy might be appropriate. Implicit in the choice of endoscopic eradication therapy for dysplasia in Barrett's esophagus, however, is the assumption that the neoplasm does not involve regional lymph nodes.

Unlike most hollow gastrointestinal organs, the esophagus has lymphatic vessels that frequently can be seen to extend into the mucosa (6). Therefore, even a neoplasm that appears to be confined to the mucosa (like HGD and intramucosal carcinoma) might have the potential to metastasize to lymph nodes through mucosal lymphatics. When considering treatment options for patients with mucosal neoplasms in Barrett's esophagus, it seems important to know how often those lesions are associated with lymph-node metastases, since such metastases would make it unlikely that endoscopic treatment could be curative. The frequency of lymph-node involvement in this situation is not clear, however, and published series of patients who had esophagectomy for HGD or intramucosal carcinoma in Barrett's esophagus have described a surprisingly wide range of frequencies for lymph-node metastases. Indeed, some investigators have found rates of unexpected lymph-node metastases so high that they recommend against endoscopic therapy for patients who are good operative risks (7). The aim of our study was to perform a systematic review to determine the rate of lymph-node metastases in patients with HGD or intramucosal carcinoma in Barrett's esophagus.

METHODS

Search strategy

We performed a systematic review using the PRISMA guidelines (8). Two members of the study team (K.B.D. and S.J.S.) searched the PubMed search engine of MEDLINE-indexed literature from the National Center for Biotechnology Information (http://www.pubmed.gov), Embase, and the CINAHL (Cumulative Index to Nursing and Allied Health Literature) for English language articles published through September 2011. We performed additional searches of MEDLINE using the Ovid Medline database. Search terms included the medical subject heading (meSH) search term "Barrett's esophagus" (also "Barrett's esophagus," "Barrett oesophagus," or "Barrett's oesophagus") combined with the keywords "lymph node," "dysplasia," "high-grade dysplasia," "intramucosal adenocarcinoma," "neoplasia," "T1," and "esophagectomy." Titles and abstracts were screened for eligibility, and potential studies meeting the inclusion criteria were reviewed. In addition, we reviewed the reference lists of selected articles to identify additional articles not retrieved by computer searches.

Study selection

We decided *a priori* to include reports that (i) included patients who had esophagectomy for HGD, intramucosal carcinoma and/or early adenocarcinoma in Barrett's esophagus; (ii) reported final surgical pathology results with at least one of the following descriptors: HGD, intramucosal carcinoma or intramucosal adenocarcinoma, pT1a, T1a, Tis, carcinoma *in situ*, mucosal cancer, or cancers involving m1, m2, m3 layers; and (iii) reported surgical pathology lymph-node status as N0 or N1, or described surgical pathology lymph-node status as positive or negative. We decided *a priori* to exclude reports that (i) did not distinguish between mucosal (T1a) and submucosal (T1b) cancers; (ii) did not distinguish esophageal adenocarcinomas from squamous cell carcinomas; (iii) did not link lymph-node status to the T stage; (iv) were single patient case reports; (v) reported only lymph-node micrometastases; (vi) included patients who had undergone preoperative radiation or chemotherapy; and (vii) stated specifically that patients had been reported in other series; in these cases, we included only the most recent or the largest series with complete data. Questions regarding the eligibility of individual reports were resolved by discussion between the reviewers. A flowchart of the search strategy and results is shown in **Figure 1**.

Data abstraction

From eligible studies, the data abstracted included the number of patients with a final pathology diagnosis of intramucosal cancer (T1a) or HGD, and the lymph-node status of these patients. For papers including the patients with both adenocarcinoma and squamous cell carcinoma, only the data pertaining to adenocarcinoma were abstracted. Likewise, in studies that included patients with more advanced esophageal adenocarcinoma (stages II–IV, T stages T1b–T4), only data pertaining to the early stage disease (T1a, HGD) were abstracted. Finally, we calculated the total number of patients, number of patients with HGD, number of patients with intramucosal carcinoma, and number of patients with lymph-node metastases.

Statistical analysis

The prevalence rates were weighted for each study's sample size and pooled with calculation of 95% confidence intervals. A secondary analysis using more restrictive inclusion criteria was also performed. The weighted prevalence rates between the primary and secondary analyses were compared using Fisher's exact test. Statistical analyses were performed using SAS (Cary, NC).

RESULTS

A total of 1,583 articles were generated from computer searches, and 10 more articles were identified through a review of reference lists. After removal of duplicate articles, 899 reports remained. Of these articles, 349 were excluded as they were review articles, case reports, guidelines, or letters to the editor, and 360 were unrelated to the topic of interest (**Figure 1**). In all, 190 full-text articles were reviewed for eligibility, and 70 met the inclusion criteria. Of the 120 excluded, the most common reasons were a lack of distinction between T1a and T1b adenocarcinomas, no link between T and N stage, a mixed population of adenocarcinoma and squamous cell carcinoma patients where T and N stages could not be

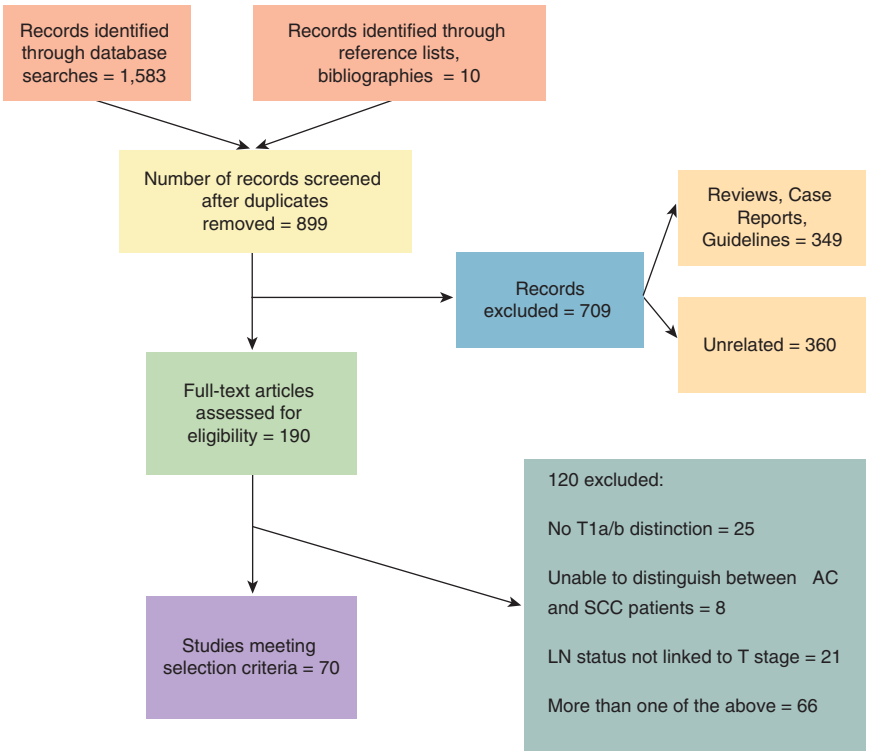

Figure 1. Search results and study selection. AC, adenocarcinoma; LN, lymph node; SCC, squamous cell carcinoma.

clearly assigned to the adenocarcinoma patients, or a combination of these factors.

Risk of lymph-node metastases for the total population of patients with HGD or intramucosal carcinoma

Among the 70 reports that met our inclusion criteria, there were a total of 1,874 patients who had a final pathology diagnosis of intramucosal adenocarcinoma or HGD (**Table 1**). Relatively few reports focused specifically on the frequency of lymph-node metastases in patients with HGD and intramucosal carcinoma. Rather, that information was gleaned from reports that focused on a number of other issues (summarized in **Table 1**) such as how the depth of tumor invasion (T stage) influenced the risk for lymph-node metastases, the accuracy of endoscopic biopsy protocols, the utility of endoscopic ultrasound for staging, and the results of different esophagectomy techniques. The total enrollment of the individual studies ranged from 8 to 359 patients and, in most reports, patients who were eligible for our analyses (i.e., patients with HGD or intramucosal carcinoma in Barrett's esophagus) comprised a relatively small minority of the total patient population. This is because many reports included patients with squamous cell carcinomas and advanced adenocarcinomas. In individual reports, the number of eligible patients ranged from 3 to 150.

Information on the number of lymph nodes resected during esophagectomy was provided in 32 of the 70 studies. The number of lymph nodes resected varied widely among the reports, ranging from a median of 0 in a series of minimally invasive, vagal-sparing esophagectomy to a median of 48 in a study of *en bloc* esophagectomy with three-field lymph-node dissection (9,10). In all, 19 of the 70 studies reported at least one patient with lymph-node metastases, with rates of positive lymph nodes ranging from 0 to 66% of all patients in the series who had esophagectomy for HGD or intramucosal carcinoma. Combining the results from all studies, 26 of 1,874 patients with HGD or intramucosal carcinoma had lymph-node metastases, for an overall rate of 1.39% (95% CI 0.86–1.92%).

Risk of lymph-node metastases for patients with HGD

Thirty-nine reports included patients who had a final pathology diagnosis of HGD (**Table 2**). The number of patients with HGD in individual studies ranged from 2 to 38, with a total of 524 patients. No patient with a final pathology diagnosis of HGD was found to have lymph-node metastases.

Risk of lymph-node metastases for patients with intramucosal adenocarcinoma

Sixty-one reports included patients who had a final pathology diagnosis of intramucosal carcinoma (**Table 3**). The number of patients with intramucosal carcinoma in individual studies ranged from 2 to 150, with a total of 1,350 patients. In all, 26 of the 1,350 patients had lymph-node metastases, for a rate of 1.93% (95% CI 1.19–2.66%).

For 15 of the 26 patients identified as having lymph-node metastases, the reports provided some description of the tumor and

Table 1. Studies of patients who had esophagectomy for intramucosal adenocarcinoma or high-grade dysplasia in Barrett's esophagus with lymph-node status reported

First author	Publication year	Study focus	Overall study size	Number of lymph nodes removed at esophagectomy, mean±s.d., (range), unless otherwise specified	Number of patients with surgical pathology showing ImCa or HGD at esophagectomy	Number of patients with HGD or ImCa and positive LN at esophagectomy	Percent of patients with HGD or ImCa and positive LN at esophagectomy
Saubier (12)	1985	Surgical treatment of AC in BE	13	NR	3	1	33.3
DeMeester (44)	1988	Surgical approach to cancer of lower esophagus and cardia	52	42±14	3	2	66.6
Reid (45)	1988	Biopsy can detect HGD and ImCa	8	NR	6	0	0
DeBaecque (21)	1990	Superficial AC in BE with HGD	50	NR	4	0	0
DeMeester (46)	1990	Surgical therapy of BE	56	NR	5	0	0
Streitz (47)	1991	Pathology of adenocarcinoma in BE	65	NR	4	0	0
Pera (48)	1992	Esophagectomy in BE with HGD	19	NR	9	0	0
Rice (49)	1993	Surgical management of BE with HGD	16	NR	15	0	0
Clark (35)	1994	*En bloc* esophagectomy for AC, nodal metastases and recurrence	43	42±20 (16–98)	6	2	33.3
Falk (50)	1994	EUS in BE with HGD	9	NR	9	0	0
Peters (51)	1994	AC outcomes in surveillance	52	NR	13	0	0
Rusch (52)	1994	Surgery for BE with HGD and early AC	27	NR	10	0	0
Holscher (22)	1995	Prognosis of early esophageal cancer	77	23 (10–48)	6	0	0
Paraf (27)	1995	Pathology of AC in BE	67	13±8 (1–35)	9	0	0
Edwards (53)	1996	Esophagectomy in BE with HGD	11	NR	3	0	0
Heitmiller (54)	1996	Esophagectomy in BE with HGD	30	NR	17	0	0
Collard (33)	1997	Radical resection for AC in BE	55	NR	12	1	8.33
Holscher (23)	1997	Early AC in BE	41	23 (10–48)	10	0	0
Ruol (55)	1997	Management of T1 AC	26	NR	3	0	0
Rice (56)	1998	Esophageal cancer depth predicts lymph-node status	359	11 (0–53)	63	1	1.59
Falk (57)	1999	Jumbo biopsies miss cancer in BE with HGD	28	NR	26	0	0
Nigro (34)	1999	Lymph-node metastases in AC	37	41 (18–82)	15	1	6.7
Nguyen (58)	2000	Minimally invasive esophagectomy for HGD	12	11.5±6.5 (0–23)	10	0	0
Stein (59)	2000	Limited resection for early AC in BE	94	Divided by time periods: early: 21 (6–48), mid: 22 (11–37), most recent: 19 (9–30)	38	0	0
Reid (60)	2000	Biopsy protocol for BE with HGD and ImCa	45	NR	33	0	0
Van Sandick (30)	2000	Pathology of early AC of esophagus and GE junction	32	13±9 (3–34)	12	0	0
Collard (61)	2001	Radical resection for AC in BE	55	NR	12	0	0

Table 1. Continued

First author	Publication year	Study focus	Overall study size	Number of lymph nodes removed at esophagectomy, mean±s.d., (range), unless otherwise specified	Number of patients with surgical pathology showing ImCa or HGD at esophagectomy	Number of patients with HGD or ImCa and positive LN at esophagectomy	Percent of patients with HGD or ImCa and positive LN at esophagectomy
Hagen (10)	2001	*En bloc* esophagectomy for AC	100	Median 48 (IQR 38.5–62)	16	1	6.25
Rice (62)	2001	Surgery for superficial esophageal AC	122	NR	91	2	2.19
Scotiniosis (63)	2001	EUS before esophagectomy for HGD and ImCa	22	10.5±5.4 (5–23)	16	0	0
Headrick (64)	2002	Esophagectomy for HGD, survival, and quality of life	54	NR	40	0	0
Fernando (65)	2002	Minimally invasive esophagectomy for HGD	28	16	23	0	0
Incarbone (66)	2002	BE surveillance and esophagectomy outcomes	97	NR	2	0	0
Dar (67)	2003	Extent of HGD and risk of AC	42	NR	38	0	0
Romagnoli (68)	2003	Esophagectomy outcomes in HGD	33	NR	25	0	0
Thomson (69)	2003	Esophagectomy for early AC and HGD	18	NR	9	0	0
Bonavina (70)	2004	Laparoscopy-assisted surgery for esophageal cancer	43	13 (8–17)	5	0	0
Buskens (20)	2004	EUS of HGD and early AC	77	NR	35	0	0
Sujendran (71)	2005	Esophagectomy for BE with HGD	17	Median 9 (3–16)	6	0	0
Reed (72)	2005	Surgical treatment of HGD	115	NR	38	0	0
Adulaimi (73)	2005	BE surveillance	37	NR	4	0	0
Liu (11)	2005	Lymph-node metastases and invasion depth in T1 AC	90	By surgery type: transthoracic: 14±11, transhiatal: 11±8	53	2	3.7
Stein (29)	2005	Lymphatic spread in early esophageal cancer, survival	290	Median 24 (6–58)	70	0	0
Westerterp (13)	2005	Surgical outcomes in early AC of esophagus and GE junction	120	8.6 (1–40)	54	1	1.85
Waxman (74)	2006	EUS in HGD and ImCa	9	NR	5	0	0
Bollschweiler (37)	2006	Lymph-node metastases in submucosal SCC and AC	60	29.2 (13–57)	14	0	0
Chang (75)	2006	BE surveillance	142	NR	23	0	0
Oh (14)	2006	Surgery for BE with ImCa	78	By surgery type: *En bloc*: median 41 (IQR 30–57), transhiatal: median 18 (IQR 11–31), vagal sparing: median 1 (IQR 0–1), transthoracic: median 20 (IQR 12–22)	23	1	4.35
Peyre (9)	2007	Vagal-sparing esophagectomy for BE with HGD and ImCa	109	By surgery type: vagal sparing: 0 (0–11), transhiatal: 19 (3–55), *En bloc* 41 (21–87)	109	0	0
Prasad (32)	2007	EMR followed by esophagectomy	25	8.7 (s.e.m. 1)	7	0	0
Williams (76)	2007	Esophagectomy outcomes for BE with HGD	38	NR	25	0	0
Ancona (18)	2008	Esophagectomy for T1 AC and SCC	98	Median 15 (IQR 11–0)	12	0	0

Table 1. Continued

First author	Publication year	Study focus	Overall study size	Number of lymph nodes removed at esophagectomy, mean±s.d., (range), unless otherwise specified	Number of patients with surgical pathology showing ImCa or HGD at esophagectomy	Number of patients with HGD or ImCa and positive LN at esophagectomy	Percent of patients with HGD or ImCa and positive LN at esophagectomy
Cen (26)	2008	Lymphovascular invasion in T1b AC	99	NR	48	2	4.16
Scheil-Bertram (25)	2008	Surgical resection for BE with AC and lymph-node metastases	29	Overall 27 (7–74), for mucosal AC: range 7–31	7	0	0
Bolton (77)	2009	Tumor length and survival in T1 AC	133	NR	64	3	4.68
Gockel (78)	2009	Esophagectomy and superficial AC and SCC	50	NR	14	1	7.14
Kariv (79)	2009	Biopsy protocol and occult neoplasia found at esophagectomy	33	NR	33	0	0
Saha (80)	2009	Laparoscopic transhiatal vs. open esophagectomy for T1 AC	44	By surgery type: Ivor-Lewis: median 19 (range 10–51), open transhiatal: median 16 (3–28), laparoscopic transhiatal: 15 (4–41)	33	0	0
Mirnezami (81)	2009	Transhiatal esophagectomy for HGD	23	NR	15	0	0
Wang (82)	2009	Prevalence of submucosal cancer in BE with HGD and ImCa	60	NR	54	0	0
Barbour (19)	2010	Early esophageal cancer lymphatic spread and prognosis	85	15 (2–39)	35	0	0
Iwanuma (83)	2010	Esophagectomy for AC and SCC	285	NR	2	0	0
Pech (16)	2010	Preoperative EUS in esophageal cancer	179	29±12.2	23	1	4.34
Sepesi (28)	2010	Prevalence of lymph-node metastases in ImCa and submucosal AC	54	Overall: 9 By surgery type: Transhiatal: 8 *En bloc*: 22	25	0	0
Bogevski (84)	2011	Comparison of esophageal cancer operations	113	By surgery type: Limited esophagectomy: 15 (range 4–41) Extended/thoracoabdominal: 24 (6–69)	29	0	0
Estrella (15)	2011	Duplicated muscularis mucosa and ImCa	99	NR	69	1	1.44
Leers (5)	2011	Lymph-node metastases in T1 AC	126	Median 34 (IQR 21–60)	75	1	1.3
Pech (24)	2011	Endoscopic vs. surgical resection of ImCa	114	Median 29 (13–57)	38	0	0
Kaneshiro (17)	2011	Duplicated muscularis mucosa in superficial BE with AC	185	NR	150	1	0.67
Zehetner (31)	2011	Endoscopic therapy vs. esophagectomy for HGD and ImCa	101	19.2	61	1	1.64
					1,874	26	1.39% (95% CI 0.86–1.92%)

AC, adenocarcinoma; BE, Barrett's esophagus; CI, confidence interval; EMR, endoscopic mucosal resection; EUS, endoscopic ultrasonography; HGD, high-grade dysplasia; ImCa, intramucosal cancer; IQR, interquartile range; LN, lymph nodes; NR, not reported; SCC, squamous cell carcinoma; s.d., standard deviation; s.e.m., standard error of the mean.
Study focus is the primary intent of the study. The overall study size is the total number of patients in the study, including the patients who do not meet the inclusion criteria for this review (e.g., have advanced adenocarcinoma or squamous cell carcinoma). The number of lymph nodes resected per patient in the overall study is reported (mean, ±s.d., range) unless otherwise specified (some studies reported the median and range). Those that did not report the number of lymph nodes resected have 'NR' listed. The number of patients with surgical pathology showing ImCa or HGD at esophagectomy, the number of HGD or ImCa patients with positive lymph nodes at esophagectomy based on surgical pathology and the percent of HGD and ImCa patients with positive lymph nodes at esophagectomy are also reported.

Table 2. Studies of patients who had esophagectomy for high-grade dysplasia in Barrett's esophagus with lymph-node status reported

First author	Publication year	Number of patients with surgical pathology showing HGD at esophagectomy	Number of patients with HGD and positive LN at esophagectomy	Percent of patients with HGD and positive LN at esophagectomy
Reid (45)	1988	4	0	0
Streitz (47)	1991	2	0	0
Pera (48)	1992	9	0	0
Rice (49)	1993	9	0	0
Falk (50)	1994	6	0	0
Peters (51)	1994	4	0	0
Rusch (52)	1994	10	0	0
Edwards (53)	1996	3	0	0
Heitmiller (54)	1996	17	0	0
Collard (33)	1997	8	0	0
Rice (56)	1998	27	0	0
Falk (57)	1999	18	0	0
Nguyen (58)	2000	7	0	0
Reid (60)	2000	19	0	0
Collard (61)	2001	12	0	0
Rice (62)	2001	38	0	0
Scotiniosis (63)	2001	14	0	0
Headrick (64)	2002	35	0	0
Fernando (65)	2002	17	0	0
Incarbone (66)	2002	2	0	0
Dar (67)	2003	18	0	0
Romagnoli (68)	2003	13	0	0
Thomson (69)	2003	4	0	0
Bonavina (70)	2004	5	0	0
Buskens (20)	2004	13	0	0
Sujendran (71)	2005	6	0	0
Reed (72)	2005	31	0	0
Stein (29)	2005	13	0	0
Westerterp (13)	2005	13	0	0
Waxman (74)	2006	4	0	0
Chang (75)	2006	14	0	0
Peyre (9)	2007	24	0	0
Prasad (32)	2007	4	0	0
Williams (76)	2007	21	0	0
Kariv (79)	2009	21	0	0
Mirnezami (81)	2009	15	0	0
Wang (82)	2009	27	0	0
Bogevski (84)	2011	4	0	0
Zehetner (31)	2011	13	0	0
		524	0	0

HGD, high-grade dysplasia; LN, lymph nodes.

Table 3. Studies of patients who had esophagectomy for intramucosal adenocarcinoma in Barrett's esophagus with lymph-node status reported

First author	Publication year	Number of patients with surgical pathology showing ImCa at esophagectomy	Number of patients with ImCa and positive LN at esophagectomy	Percent of patients with ImCa and positive LN at esophagectomy
Saubier (12)	1985	3	1	33.3
DeMeester (44)	1988	3	2	66.6
Reid (45)	1988	2	0	0
DeBaecque (21)	1990	4	0	0
DeMeester (46)	1990	5	0	0
Streitz (47)	1991	2	0	0
Rice (49)	1993	6	0	0
Clark (35)	1994	6	2	33.3
Falk (50)	1994	3	0	0
Peters (51)	1994	9	0	0
Holscher (22)	1995	6	0	0
Paraf (27)	1995	9	0	0
Collard (33)	1997	4	1	25
Holscher (23)	1997	10	0	0
Ruol (55)	1997	3	0	0
Rice (56)	1998	36	1	2.8
Falk (57)	1999	8	0	0
Nigro (34)	1999	15	1	6.7
Nguyen (58)	2000	3	0	0
Stein (59)	2000	38	0	0
Reid (60)	2000	14	0	0
Van Sandick (30)	2000	12	0	0
Hagen (10)	2001	16	1	6.25
Rice (62)	2001	53	2	3.77
Scotiniosis (63)	2001	2	0	0
Headrick (64)	2002	5	0	0
Fernando (65)	2002	6	0	0
Dar (67)	2003	20	0	0
Romagnoli (68)	2003	12	0	0
Thomson (69)	2003	5	0	0
Buskens (20)	2004	22	0	0
Reed (72)	2005	7	0	0
Adulaimi (73)	2005	4	0	0
Liu (11)	2005	53	2	3.7
Stein (29)	2005	57	0	0
Westerterp (13)	2005	41	1	2.44
Waxman (74)	2006	1	0	0
Bollschweiler (37)	2006	14	0	0
Chang (75)	2006	9	0	0
Oh (14)	2006	23	1	4.35
Peyre (9)	2007	85	0	0

Table 3. Continued

First author	Publication year	Number of patients with surgical pathology showing ImCa at esophagectomy	Number of patients with ImCa and positive LN at esophagectomy	Percent of patients with ImCa and positive LN at esophagectomy
Prasad (32)	2007	3	0	0
Williams (76)	2007	4	0	0
Ancona (18)	2008	12	0	0
Cen (26)	2008	48	2	4.16
Scheil-Bertram (25)	2008	7	0	0
Bolton (77)	2009	64	3	4.68
Gockel (78)	2009	14	1	7.14
Kariv (79)	2009	12	0	0
Saha (80)	2009	33	0	0
Wang (82)	2009	27	0	0
Barbour (19)	2010	35	0	0
Iwanuma (83)	2010	2	0	0
Pech (16)	2010	23	1	4.34
Sepesi (28)	2010	25	0	0
Bogevski (84)	2011	25	0	0
Estrella (15)	2011	69	1	1.44
Leers (5)	2011	75	1	1.30
Pech (24)	2011	38	0	0
Kaneshiro (17)	2011	150	1	0.67
Zehetner (31)	2011	48	1	2.08
		1,350	26	1.93% (95% CI 1.19–2.66%)

CI, confidence interval; HGD, high-grade dysplasia; ImCa, intramucosal adenocarcinoma; LN, lymph nodes.

lymph nodes. Among nine patients for whom detailed information on the depth of tumor invasion was available, eight had m3 tumors (which involve, but do not penetrate through, the muscularis mucosae) and one patient had an m2 lesion (involving the lamina propria but not the muscularis mucosae) (5,11–17). Among the 12 studies that reported the depth of mucosal tumor invasion as m1/m2/m3, there were a total of 170 patients with m3 lesions, 8 of whom (4.7%) had lymph-node metastases (5,11,13,14,18–25).

Twelve studies provided data on the frequency of lymphovascular invasion in patients with intramucosal adenocarcinoma, which ranged from 0 to 18% (5,11,15,16,19,20,26–31). Among the 26 patients with lymph-node metastases, lymphovascular invasion was described specifically in only two (5,16). Tumor size and grade together were described for only 1 of the 26 patients with lymph-node metastases; that patient had a 2.2-cm tumor that was poorly differentiated (5).

Six studies specifically reported data on the presence of the duplicated muscularis mucosae in the resected Barrett's esophagus (5,13,15,17,19,32). For patients with intramucosal carcinoma in these studies, the frequency of finding the duplicated muscularis mucosae ranged from 32 to 65%. There was no apparent association between the presence of the duplicated muscularis mucosae and the presence of metastatic lymphadenopathy (5,13,17,19).

Among 10 patients for whom the number of positive lymph nodes was reported, 9 had only a single lymph node involved (5,10,12,14,17,31,33–35). For 21 of the 26 patients with lymph-node metastases, the report did not specify whether the involved lymph nodes were loco-regional or distant; among 5 patients for whom this information was provided, all involved nodes were loco-regional (10,17,33,35).

Secondary analysis

A number of individual reports included in this systematic review are from the same institution and share some of the same authors. This raises the possibility that some of the same patients were included in multiple reports, and it is not clear how this would affect the outcome of our systematic review. To minimize this possibility, we performed another analysis that included only one report of the largest study from each institution, unless the article provided sufficient information to exclude the possibility of patient overlap. We identified 35 such reports that included a total of 967 patients with HGD or intramucosal cancer. Twelve of these

patients had lymph-node metastases, for a rate of 1.24% (95% CI 0.54–1.94%). Among the 259 patients with a final pathology diagnosis of HGD, none had positive lymph nodes. Among the 708 patients with a final pathology diagnosis of intramucosal cancer, 12 (1.70%, 95% CI 0.74–2.65%) had lymph-node metastases. The frequency of lymph-node metastases in this analysis that included only one report per institution did not differ significantly from the analysis that included all reports in the systematic review (1.39% vs. 1.24%, $P=0.65$ for all patients with HGD and intramucosal carcinoma, 1.93% vs. 1.70%, $P=0.62$ for patients with intramucosal carcinoma).

DISCUSSION

Our systematic review identified 70 reports that described surgical pathology findings for 1,874 patients who had esophagectomy performed because of HGD or intramucosal carcinoma in Barrett's esophagus. Lymph-node metastases were found in 26 (1.39%) of those patients. No lymph-node metastases were found in the 524 patients who had a final pathology diagnosis of HGD, whereas 26 (1.93%) of the 1,350 patients with a final pathology diagnosis of intramucosal carcinoma had positive lymph nodes. These results did not change significantly in a secondary analysis performed to minimize the possibility that the same patients might have been included in more than one report.

Our findings might suggest that HGD in Barrett's esophagus has virtually no risk of lymph-node metastases. However, it is important to emphasize that our estimates on the frequency of lymph-node metastases are based on a systematic review of final pathology diagnoses that were rendered after examination of esophagectomy specimens. Caution should be exercised in extrapolating these results to predict the frequency of lymph-node metastases in patients found to have HGD or intramucosal carcinoma in endoscopic biopsy specimens of Barrett's metaplasia. Substantial disagreement among gastrointestinal pathologists has been reported in distinguishing HGD from intramucosal carcinoma in such biopsy specimens (36). In equivocal cases, the absence of lymph-node metastases in an esophagectomy specimen might persuade a pathologist to make a diagnosis of HGD rather than intramucosal carcinoma. Alternatively, the presence of positive lymph nodes might bias that pathologist to make a diagnosis of intramucosal carcinoma rather than HGD.

Histopathological features of mucosal neoplasms that might affect the risk of lymph-node metastases include the depth of tumor invasion, the presence of lymphovascular invasion, and the degree of tumor differentiation. For T1b tumors, which penetrate through the muscularis mucosae, it is well established that the frequency of lymph-node metastases increases with the depth of tumor invasion into the submucosa. For example, lymph-node metastases have been found in 9–20% of patients with sm1 tumors (which involve only the upper one-third of the submucosa), whereas 24–50% of patients with sm3 tumors (which involve the deepest one-third of the submucosa) have positive lymph nodes (17,19,28). Our systematic review suggests that depth of invasion is also a risk factor for lymph-node metastases in T1a tumors, which do not penetrate the muscularis mucosae. Although we found only 12 studies that reported the depth of mucosal tumor invasion as m1/m2/m3, 8 of the 170 total patients with m3 lesions (4.7%) had lymph-node metastases (5,11,13,14,18–25). In more advanced esophageal adenocarcinomas, lymphovascular invasion and poor tumor differentiation are well-established risk factors for metastatic disease (27,37). For patients with mucosal neoplasms in Barrett's esophagus, however, our systematic review revealed insufficient data to determine whether lymphovascular invasion and poor tumor differentiation significantly increase the risk of lymph-node metastases.

Histological evaluation of the esophagus resected for dysplasia or cancer in Barrett's esophagus has revealed duplication of the muscularis mucosae in up to 92% of cases (42). This finding is important because duplication of the muscularis mucosae can result in errors in the staging of superficial adenocarcinomas. Typically, the result is overstaging because the pathologist assumes mistakenly that tumor found below the more superficial of the two muscularis mucosae is involving the submucosa. Among the 70 reports included in our systematic review, only 6 provided data on the frequency of finding the duplicated muscularis mucosae in the resected Barrett's esophagus, which ranged from 32 to 65% (5,13,15,17,19,32). The presence of the duplicated muscularis mucosae should not affect the detection of lymph-node metastases at esophagectomy, and we found no association between the presence of the duplicated muscularis mucosae and the presence of such metastases.

Our study suffers from the limitations inherent in a retrospective review of published data. Few of the reports included in our study had focused specifically on the frequency of lymph-node metastases in patients with HGD and intramucosal carcinoma. Different surgeons used different techniques for esophagectomy. The number of lymph nodes removed during this operation can range from 0 to >50 (38), and the chances for detecting positive lymph nodes increases as the number of nodes resected increases. There was no standardized protocol for pathology review of the esophagectomy specimens, and differences among institutions in the thoroughness of this review are likely to influence the frequency of finding lymph-node metastases.

A number of the reports included in our review predate the widespread availability of EMR and endoscopic ultrasonography (EUS), and there was no standardized protocol for their application in studies conducted when these techniques were available. It is not clear how the preoperative use of these techniques would influence the frequency of finding lymph-node metastases at esophagectomy. EMR is better than endoscopic biopsy for detecting submucosal invasion of cancer in Barrett's esophagus (39). Therefore, the use of EMR is likely to improve the accuracy of the preoperative diagnosis of HGD and intramucosal carcinoma. However, our systematic review focused on the final pathology report after an examination of the resected esophagus, and the availability of EMR is unlikely to have influenced those results. Today, the preoperative use of EUS might

influence the frequency of finding lymph-node metastases at esophagectomy for patients with HGD and intramucosal carcinoma, because only patients found to have malignant lymph nodes by EUS would be likely to have esophagectomy. Without positive lymph nodes demonstrated by EUS, the large majority of patients with HGD and intramucosal cancer now would be treated with endoscopic eradication therapy. Therefore, the preoperative use of EUS might be expected to increase the likelihood of finding lymph-node metastases at esophagectomy. Reports on the utility of EUS for the detection of malignant lymph nodes have described a wide range of sensitivities and specificities (16), however, and a false-positive EUS diagnosis of lymph-node metastases might result in esophagectomy with the finding of negative lymph nodes. Thus, it is not entirely clear how the preoperative EUS would influence the frequency of positive lymph nodes at esophagectomy.

With some cancers, such as renal cell carcinoma, there are rare reports of metastases resolving spontaneously after resection of the primary tumor (40). We are unaware of any such reports for esophageal adenocarcinoma, and spontaneous resolution of metastases from this cancer seems unlikely. Therefore, endoscopic eradication therapy cannot be considered curative for patients with mucosal cancers in Barrett's esophagus that have metastasized to regional lymph nodes. Such patients might be cured by an operation that removes the malignant nodes, or by the use of chemotherapy or radiation therapy aimed at lymph-node metastases. These treatments can be associated with substantial morbidity and mortality, however, and none can guarantee a cure for patients with metastatic esophageal adenocarcinoma.

Our systematic review suggests that the risk of lymph-node metastases for patients with mucosal neoplasms in Barrett's esophagus is in the range of 1–2%. Despite this potential for metastatic disease, several tertiary referral centers have reported excellent long-term results for endoscopic eradication therapy of mucosal Barrett's neoplasms (41–43). Metachronous neoplasms, presumably due to incomplete obliteration of the mucosal tumors, occurred frequently in those series, but those metachronous lesions generally responded readily to repeat endoscopic eradication therapy. However, a careful review of these reports reveals that some patients died from metastatic esophageal adenocarcinoma. In Pouw's series of 169 patients with mucosal neoplasms in Barrett's esophagus who were treated endoscopically and followed for a median of 32 months, one patient (0.6%) died of metastatic esophageal cancer (41). Prasad *et al.* (42) compared the outcomes of endoscopic and surgical treatments for patients with intramucosal carcinoma. During a mean follow-up of 64 months, 1 of 132 patients (0.8%) treated endoscopically died of metastatic disease. It should be noted, however, that 1 of 46 patients (2.1%) in the surgical group also died of metastatic esophageal cancer even though no positive lymph nodes were found in the resection specimen. In Pech's series of 349 patients with mucosal neoplasms in Barrett's esophagus, there were no deaths from metastatic cancer during a mean follow-up of 63.6 months (43). However, there were 58 patient deaths (not tumor related) during that time, and 13 patients eventually had esophagectomy because endoscopic therapy had failed. With such a high rate of dropout due to non-cancer deaths and surgery, a low rate of metastatic disease easily could have been missed. These low rates of metastatic cancer for highly selected patients in tertiary referral centers support the findings of our systematic review that mucosal neoplasms in Barrett's esophagus do metastasize, albeit infrequently.

We feel it is important that patients and clinicians appreciate that there is a small but real risk of lymph-node metastases associated with mucosal neoplasms in Barrett's esophagus. Our systematic review suggests that this risk is in the range of 1–2%. Thus, patients who opt for endoscopic eradication therapy have at least a 1–2% chance that this treatment will not be curative. The alternative treatment is esophagectomy. For older patients who have serious comorbid illnesses, the risks of esophagectomy clearly outweigh the risks of lymph-node metastases. For younger and otherwise healthy patients with HGD and intramucosal carcinoma in Barrett's esophagus, the mortality of esophagectomy probably exceeds 2%, and the procedure is associated with considerable long-term morbidity (3). As discussed above, furthermore, it is not clear that esophagectomy will be curative for patients with lymph-node metastases. It has been suggested that physicians should consider a number of factors (e.g., patient's age, co-morbidities, extent of metaplasia and neoplasia) when deciding between endoscopic and surgical therapies for mucosal neoplasms in Barrett's esophagus, and we agree that the choice should be individualized. However, our systematic review suggests that the risk of lymph-node metastases alone does not warrant the choice of esophagectomy over endoscopic therapy.

CONFLICT OF INTEREST

Guarantor of the article: Kerry B. Dunbar, MD.

Specific author contributions: Performed the literature search, reviewed the articles, performed data abstraction, wrote the manuscript, and approved the final draft submitted: Kerry B. Dunbar; participated in identifying papers for the study, reviewed the articles, the search, edited the manuscript, and approved the final draft submitted: Stuart Jon Spechler.

Financial support: This work was supported by the Office of Medical Research, Department of Veterans Affairs and the National Institutes of Health (R01-CA134571).

Potential competing interests: None.

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