Advances in imaging and endoscopic therapy in Barrett’s esophagus
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Risk of lymph node metastases in deeper invading early adenocarcinoma of the esophagus and cardia: a study based on endoscopic resection specimens

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Part II: Endoscopic therapy in Barrett’s esophagus

Abstract

Introduction: Most lymph node metastases risk estimations in adenocarcinoma of the esophagus and cardia (AEC) with invasion in the muscularis mucosae (m3) or submucosa are based on surgical series. **Aim:** To correlate m3 and submucosal infiltration depth of AEC in endoscopic resection (ER) specimens with the rate of lymph node metastases. **Methods:** Patients undergoing ER for AEC between January 2000 and March 2008 in 2 centers were included if the ER specimen showed m3 or submucosal cancer. Infiltration in the muscularis mucosae was defined as m3. Submucosal invasion was classified as sm1 (≤500μm) or sm2/3 (>500μm). Exclusion criteria were chemo/radiotherapy and irradical ER. **Results:** A total of 82 patients were included: 57 showed m3, 12 sm1 and 13 sm2/3. Thirteen tumors were poorly differentiated and 5 showed lymphovascular invasion. After initial ER, 7 patients underwent surgery and 75 endoscopic therapy. No lymph node metastases were found in 158 lymph nodes of the esophagectomy specimens and none of the endoscopically treated patients were diagnosed with lymph node metastases during a median follow-up of 26 months (IQR 14-41). **Conclusions:** This study suggests that lymph node metastases risk for m3 and submucosal AEC may be lower than assumed by surgical series and that current guidelines are valid as it comes to including m3 AEC for endoscopic therapy. This study may also suggest that selected patients with submucosal cancers are eligible for endoscopic management as well. Confirmation of these results is needed in larger series with longer follow-up.
Introduction

Adenocarcinoma of the esophagus and the gastric cardia (AEC) is a rapidly rising form of cancer in the Western world.\textsuperscript{1,2} The last decade endoscopic resection (ER) has become the treatment of choice for selected patients with early AEC.\textsuperscript{3-7} ER is safe, effective and significantly less invasive compared to esophageal resection, which is associated with a mortality of 3-5% and a significant morbidity rate even in expert centers.\textsuperscript{8} Although radical resection of mucosal as well as submucosal tumors is technically feasible with ER, endoscopic therapy is only considered to be adequate if the chance of lymph node metastasis (LNM) is lower than the surgical mortality rate of the esophagectomy. The risk of LNM increases with the infiltration depth of the tumor. In order to stratify this risk, mucosal and submucosal infiltration can be further subdivided (Figure 1).

Studies in esophageal squamous cancer (ESC) have shown that infiltration into the epithelium (m1) and lamina propria (m2) are clear indications for ER. ESC infiltrating the muscularis mucosae (m3) and the upper third of the submucosa (sm1) are only considered relative indications, as the risk of LNM here is around 19%.\textsuperscript{9-14}

![Figure 1](https://example.com/fig1.png)

**Figure 1** Subclassification of tumor infiltration in the mucosa and submucosa. HGIN High grade intraepithelial neoplasia; m2 invasion in the lamina propria; m3 invasion into the muscularis mucosae; sm1 submucosal ≤500μm; sm2 submucosal >500μm≤1000μm; sm3 submucosal invasion >1000μm; ep epithelium; lp lamina propria; mm muscularis mucosae; sm submucosa. For the purpose of this study sm2 and sm3 cases were grouped into 1 category (sm2/3).
AEC is considered to have a lower risk of LNM compared to ESC. For mucosal AEC the overall chance of LNM is virtually 0%. Little is however known about the specific risk of infiltration in each part of the mucosa. Subdivision of the mucosa into high grade intraepithelial neoplasia, m2 and m3 AEC and their correlation with LNM has only be reported by a few retrospective surgical series, which report 4-12% LNM in m3 AEC. The reported rates of LNM in submucosal AEC vary between 16 to 41%. Again these retrospective surgical series report increasing LNM rates with infiltration depth, varying from 0 to 22% for AEC invading into the upper third of the submucosa (sm1) and from 36 to 54% for AEC infiltrating the middle and lower third of the submucosa (sm2/3).

Retrospective surgical series mainly included patients in a time period when exact depth of tumor infiltration had little clinical relevance for subsequent patient management. Surgical resection specimens were generally routinely cut in 5-mm slices. Consequently the area with the deepest infiltration may easily have been missed resulting in an underestimation of the invasion depth. As a result, rates of LNM assumed to correspond to a certain invasion depth, may actually correspond with deeper invading lesions. This is in sharp contrast with the histological evaluation of ER specimens, which are routinely cut in 2-mm slices. For submucosal invading lesions additional slides are cut from the tissue block of interest, allowing for thorough histological assessment and a more accurate estimation of tumor invasion depth.

In current practice, decisions on patient management are based on the histological assessment of the ER specimen. The aim of this study was therefore to evaluate the risk of LNM in deeper invading early AEC by correlating m3, sm1 and sm2/3 invasion assessed in the ER-specimen with the presence of LNM detected either during subsequent esophagectomy or during endoscopic follow-up.

**Methods**

**Patients**

For this retrospective cohort study all consecutive patients who underwent an ER for adenocarcinoma in the esophagus or cardia with invasion into the muscularis mucosae (m3) or invasion into the submucosa (sm1 and sm2/3) were included. The endoscopic resections were performed in the Academic Medical Center (Amsterdam) and the Sint Antonius Hospital (Nieuwegein) in the Netherlands between January 2000 and March 2008.

Patients were excluded if they received chemo/radiotherapy within 6 months after ER or if ER was irradical. ER was considered irradical if the ER specimen showed cancer in the vertical
resection margin or if the endoscopist was not able to completely remove all lesions suspicious for cancer. Irradical ER was selected as exclusion criterion since the infiltration depth can not properly be assessed when the vertical margin of the ER specimen is tumor positive. In case of remaining lesions suspicious for carcinoma, patients who were not referred for surgery were excluded because LNM that develop during follow-up can not conclusively be related to the initially resected lesion or residual remaining cancer.

Prior to ER patients were screened for regional LNM with endoscopic ultrasonography (EUS) and for distant metastasis with CT-scan or an X-ray of the thorax and abdominal ultrasound.

**ER**

All patients underwent ER under conscious sedation (intravenous midazolam in combination with fentanyl or pethidine) as out-patient procedures. After inspection and marking of the lesion, ER was performed using the ER-cap technique (after submucosal lifting), or the multiband mucosectomy technique. Lesions with a diameter <2 cm were resected en-bloc, larger lesions were resected in multiple pieces. All resected specimens were retrieved, pinned down on paraffin with the mucosal side up, and fixed in formalin for histological evaluation. No attempts were made to reconstruct the piecemeal resections.

**Histology**

ER specimens were cut into 2-mm slices, and cut in 4 μm slides for standard haemotoxilin & eosin staining. During routine evaluation two pathologists classified abnormalities according to the WHO classification and disagreement was resolved by consensus. For the purpose of this study, all slides of ER specimens with submucosal invasion, poorly differentiated cancer, or lymphovascular invasion (LVI) according to the initial pathology report were revised by an expert gastro-intestinal pathologist (FtK). The following characteristics were assessed: submucosal invasion depth in micrometers (from deepest muscularis mucosae till deepest tumor infiltration in submucosa), differentiation grade, LVI, involvement of the deeper resection margin, and involvement of the lateral margins in the case of en-bloc resections.

Invasion depth was defined as m3 if the tumor infiltrated into the muscularis mucosae. In the case of a doubled muscularis mucosae, infiltration in the superficial muscularis mucosae or between both muscularis mucosae or in the deepest muscularis mucosae layer was defined as m3. If the tumor infiltrated beyond the deepest muscularis mucosae it was considered submucosal. Submucosal invasion ≤500 μm into the submucosa was defined as sm1. If tumor invasion was >500 μm into the submucosa the lesion was defined as sm2/3.
Further management after the initial ER
After the initial ER of the tumor, further treatment was tailored for each patient depending on the histology of the ER specimens, highest grade of neoplasia in biopsies of residual Barrett mucosa and comorbidity. The following guidelines were used for further management after ER:

1. Patients with well to moderately differentiated mucosal cancers without LVI were managed endoscopically
2. Patients with submucosal invasion, poorly differentiated cancers and/or LVI were treated surgically when fit for surgery.
3. Patients meeting the selection criteria for surgery but unfit for surgery were generally managed endoscopically.

Additional endoscopic management included the following alternatives:

1. Complete endoscopic removal of all lesions suspicious for cancer and complete histological removal of all neoplasia and intestinal metaplasia.
2. Complete endoscopic removal of all lesions suspicious for cancer and complete histological removal of all neoplasia.
3. Complete endoscopic removal of all lesions suspicious for cancer.

Additional endoscopic therapy consisted of ER of lesions suspicious for cancer, stepwise radical endoscopic resection, 5-aminolevulinic acid photo dynamic therapy (PDT), argon plasma coagulation (APC) and/or radiofrequency ablation (RFA), according to the protocols at that time. Patients who were referred for surgery were treated with either transhiatal or transthoracic esophageal resection with gastric tube reconstruction.

Follow-up
Follow-up data of patients were retrieved until March 2009 or until death. In general, after endoscopic treatment was considered complete, patients were followed endoscopically every 3 to 6 months within the first year and every 6-12 months thereafter. Endoscopic follow-up consisted of endoscopic inspection of the esophagus with biopsies and annual EUS with fine needle aspiration (FNA) in the case of suspicious lymph nodes. If surgery had been performed, patients were followed clinically every 3 to 6 months during the first year and every 6 months thereafter at the outpatient clinic. Additional examination was only performed in case of symptoms.

Data collection for this study
From all included patients data on medical history, endoscopic procedures, histology, radiology, and visits to the outpatient clinic after the first ER were collected from the medical records and documented on a standardized case record form. If follow-up was incomplete the referring hospital or general practitioner was contacted to provide the missing data.
Endpoints

The primary endpoint of this study was the diagnosis of LNM. In the case of an esophagectomy, the primary endpoint was the presence of LNM evaluated in surgical resection specimens. In the case of endoscopic therapy, the primary endpoint was the presence of any extraesophageal cancer recurrence detected during follow-up with EUS, CT-scan or other imaging techniques. Secondary endpoints were death and the local occurrence of the cancer in the esophagus, i.e. intraesophageal cancer, during follow-up after ER confirmed on pathology.

Statistical methods

Statistical analysis was performed with a statistical software package (Statistical Package for the Social Sciences 14.0.2; SPSS Inc, Chicago, IL, USA). Data with a skewed distribution were described with the median and interquartile ranges (IQR). Differences in proportions for a poor differentiation grade between mucosal and submucosal infiltration and differences in proportions for LVI between well/moderately and poorly differentiated tumors were tested with the Fisher exact test. Confidence intervals of the proportions were calculated with the Confidence Interval Analysis package.32

Results

Patients

A total of 115 patients underwent ER between January 2000 and March 2008 and were found to have an adenocarcinoma of the esophagus or cardia invading into the muscularis mucosae (m3) or the submucosa. Seven patients were excluded because of chemo/radiotherapy within 6 months after ER (3 for a second extraesophageal primary tumor and 4 for irradical ER) and 26 had residual tumor after ER (22 had tumor positive vertical margins of the ER specimen, 4 had lesions suspicious for cancer left in the esophagus). Characteristics of the remaining 82 patients are shown in Table 1. By March 2009, all patients have completed their surgical or endoscopic treatment. In case of surgery, esophageal resection was performed transhiatal in 3 patients and transthoracic in 4 patients. In case of endoscopic therapy, endoscopic management was to remove the whole Barrett segment in 48 patients (64%), to endoscopically remove all lesions suspicious for cancer and histological all (intraepithelial) neoplasia in 6 patients (8%) and to endoscopically remove all lesions suspicious for cancer in 21 patients (28%).
Table 1. Patient and tumor characteristics.

<table>
<thead>
<tr>
<th>Patients n=64</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years at ER of lesion</td>
<td>70 yrs (IQR 59-78)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Barrett</td>
<td>75</td>
</tr>
<tr>
<td>Cardia</td>
<td>7</td>
</tr>
<tr>
<td>Barrett length</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>4 cm (IQR 1-8)</td>
</tr>
<tr>
<td>M</td>
<td>6 cm (IQR 4-9)</td>
</tr>
<tr>
<td>Infiltration depth</td>
<td></td>
</tr>
<tr>
<td>m3</td>
<td>57</td>
</tr>
<tr>
<td>sm1 (≤500μm)</td>
<td>12</td>
</tr>
<tr>
<td>sm2/3 (&gt;500μm)</td>
<td>13</td>
</tr>
<tr>
<td>Differentiation grade</td>
<td></td>
</tr>
<tr>
<td>G1/2</td>
<td>69</td>
</tr>
<tr>
<td>G3</td>
<td>13</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>77</td>
</tr>
<tr>
<td>Present</td>
<td>5</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
</tr>
<tr>
<td>Endoscopic</td>
<td>75</td>
</tr>
<tr>
<td>Surgery</td>
<td>7</td>
</tr>
</tbody>
</table>

IQR inter-quartile range; C circumferential extent; M maximum extent; m3 invasion in the muscularis mucosae; sm1 submucosal invasion ≤500μm; sm2/3 submucosal invasion >500μm; G1/2 good or moderate differentiation grade; G3 poor differentiation grade; LVI lymphovascular invasion.

Histological outcome of initial ER

In the ER specimens, m3 adenocarcinoma was diagnosed in 57 patients, 52 were well/moderately differentiated without LVI and 5 were poorly differentiated showing LVI in 3. Sm1 adenocarcinoma was present in 12 patients with a median infiltration depth of 200 μm (IQR 100-300), 9 were well/moderately differentiated showing LVI in 1 and 3 were poorly differentiated without LVI. Sm2/3 adenocarcinoma was present in 13 patients with a median infiltration depth of 900 μm (IQR 800-1100), 8 were well/moderately differentiated without LVI and 5 were poorly differentiated showing LVI in 1.

Submucosal invasion of the cancer was associated with a poor differentiation (p=0.02). Poorly differentiated tumors were significantly more often associated with LVI (p=0.002).

Lymph node metastases: esophagectomy specimen

After the initial ER, 7 of the 82 patients were referred for surgery (Figure 2). Patients underwent surgery after a median time of 2 months (IQR 1-3 months) after the initial ER. No LNM was found in a total of 158 lymph nodes in the esophagectomy specimens. The median number of resected lymph nodes per patient was 17 (IQR 11-40). In all patients the deepest infiltration depth of the tumor was diagnosed at the initial ER. The esophagectomy specimen showed no residual tumor except in one patient who had a sm2/3 tumor in the diagnostic ER specimen and a residual m3
adenocarcinoma in the esophagectomy specimen (Table 2 and 3). During a median follow-up of 33 months (IQR 23-59) after surgery no recurrences were seen.

Figure 2: Patient flow-chart. AEC adenocarcinoma of the esophagus and cardia; m3 invasion into the muscularis mucosae; sm submucosal invasion; ER endoscopic resection; FU follow-up; IQR inter quartile range; sm1 submucosal invasion ≤500μm; sm2/3 submucosal invasion >500μm; Tx therapy.

Table 2. Histological outcome of the ER specimens and surgical resection specimens in the 8 patients who were referred for surgery after the initial ER.

<table>
<thead>
<tr>
<th>Pathology ER specimen</th>
<th>Pathology surgery specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Deeper margin</td>
</tr>
<tr>
<td>sm1 Free</td>
<td>G2</td>
</tr>
<tr>
<td>sm1 Free</td>
<td>G2</td>
</tr>
<tr>
<td>sm1 Free</td>
<td>G2</td>
</tr>
<tr>
<td>sm2/3 Free</td>
<td>G2</td>
</tr>
<tr>
<td>sm2/3 Free</td>
<td>G2</td>
</tr>
<tr>
<td>sm2/3 Free</td>
<td>G3</td>
</tr>
<tr>
<td>sm2/3 Free</td>
<td>G3</td>
</tr>
</tbody>
</table>

ER endoscopic resection; sm1 submucosal invasion ≤500μm; sm2/3 submucosal invasion >500μm; G2 moderate differentiation; G3 poor differentiation; LVI lymphovascular invasion; TTECR trans-thoracic esophage resection; HGIN high grade intraepithelial neoplasia; LGIN low grade intraepithelial neoplasia; m3 invasion into the muscularis mucosae; IN intraepithelial neoplasia; FU follow-up.

Operation and post operative follow-up: "Academic Medical Center; "Sint Antonius Hospital; "Elsewhere

Lymph node metastases: extraesophageal cancer recurrence during follow-up

After the initial ER, 75 of the 82 patients were further managed endoscopically (Figure 2). During a median follow-up of 26 months (IQR 14-41) none of the 75 endoscopically treated patients were diagnosed with extraesophageal cancer recurrence, suggesting absence of extraesophageal disease at the time of the initial ER (Table 3).
Table 3. Rate of lymph node metastasis for m3, sm1 and sm2/3 adenocarcinoma of esophagus and cardia

<table>
<thead>
<tr>
<th>Positive lymph nodes</th>
<th>Rate of LNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>m3</td>
<td>0/57 0% (95% CI 0-6%)</td>
</tr>
<tr>
<td>sm1</td>
<td>0/12 0% (95% CI 0-27%)</td>
</tr>
<tr>
<td>sm2/3</td>
<td>0/13 0% (95% CI 0-25%)</td>
</tr>
</tbody>
</table>

m3 invasion in the muscularis mucosae; sm1 submucosal invasion ≤500μm; sm2/3 submucosal invasion >500μm; LNM lymph node metastasis

Follow-up
Follow-up was ended prematurely in 17 patients after a median of 22 months (IQR 10-44): Eleven patients died because of tumor unrelated causes, in three patients follow-up was stopped because of severe co-morbidity and two patients started with chemotherapy for a second tumor outside the esophagus or cardia. One patient died because of an intraesophageal cancer occurring during follow-up after ER that was treated conservative as the patient was unfit for surgery (see below).

Occurrence of intraesophageal cancer during follow-up
During follow-up of the 75 endoscopically treated patients, intraesophageal cancer occurred in 4 of the 57 (7%) patients with an initial m3 tumor, in none of the 9 patients with sm1, and in 3 of the 9 (33%) patients with sm2/3. Cancer developed in the remaining Barrett segment after focal ER (n=3), in the neo-z-line after removal of the whole Barrett segment (n=3) and in the cardia (n=1) after a median follow-up of 13 months (IQR 8-39). All were managed endoscopically except for two. One patient was referred for surgery because of a cancer that developed 8 months after ER of a poorly differentiated m3 cancer with LVI. The surgical specimen showed a T4N1 cancer and the patient developed distant metastases 7 months after surgery. The second patient developed a locally advanced intraesophageal cancer 43 months after ER of a sm2/3 cancer. This patient was managed conservatively because of co-morbidity and died 22 months after this second cancer was diagnosed.

Discussion
In this study we have evaluated the rate of lymph node metastases (LNM) in 82 patients who underwent endoscopic resection of adenocarcinoma of the esophagus or cardia (AEC) invading into the muscularis mucosae (m3) or the submucosa in the corresponding endoscopic resection specimens. Surgical resection specimens and follow-up after endoscopic treatment were used to evaluate the presence of LNM. No LNM were detected in any of the patients who underwent esophagectomy after the ER and none of the patients who were treated endoscopically had
Lymph node metastasis risk of submucosal adenocarcinoma detected during a median follow-up of 26 months. These data suggest that endoscopic management may be appropriate for m3 AEC and for selected cases with superficial submucosal invasion.

Our data are in accordance with the findings of Manner et al. who reported on a prospective series of 21 Barrett’s patients, with ‘low risk’ well differentiated sm1 cancer without signs of LVI diagnosed in the initial ER specimen. No LNM was found in any of the patients after a median follow-up of 62 months.33 These data are however in contrast with some retrospective surgical series which have reported higher risk estimates of LNM in AEC, ranging from 4% to 12% for m3, from 0% to 22% for sm1 and from 36% to 54% for sm2/3 AEC.16-19, 22 These studies may, however, have overestimated the risk of LNM because of several reasons. First, as mentioned in the introduction, retrospective surgical series mainly included patients in a time period when exact depth of tumor infiltration had little clinical relevance for subsequent patient management. Second, surgical specimens are routinely cut in slices with larger intervals than ER specimens. As a result, rates of LNM, assumed to correspond to a certain invasion depth, may actually correspond with deeper invading lesions. Another possible reason for overestimation of LNM in m3 and submucosal AEC in surgical series is the absence of differentiation between patients with enlarged lymph nodes and patients with normal lymph nodes on EUS. Patients with enlarged lymph nodes on EUS will most likely show a higher rate of LNM than patients with normal lymph nodes on EUS. Our study includes basically only patients with normal lymph nodes on EUS. A properly designed retrospective study using surgical resection specimens should therefore only include patients with normal EUS at baseline and complete dedicated review of the original tissue blocks for the true invasion depth of the tumor. None of the above referenced surgical series meets all these criteria and the lowest rate of LNM was found in a study in which indeed the resection specimens underwent a dedicated histological re-evaluation.16

Several definitions have been proposed to subdivide AEC infiltration in the muscularis mucosae in case of a doubled muscularis mucosae.16, 34 In the current study infiltration in the superficial muscularis mucosae or between both muscularis mucosae or in the deepest muscularis mucosae layer were all considered to be m3. This definition was used as in clinical practice it was not always easy to distinguish all these different layers of a doubled muscularis mucosae. In addition, it seems not to have clinical relevance to subdivide the doubled muscularis mucosae as no LNM were found in case of EAC infiltrating the muscularis mucosae.

Although the main focus of this study was the detection of LNM, we can not ignore the two patients that developed after ER an advanced cancer during follow-up: one occurring after ER of a sm2/3 tumor and one after ER of a poorly differentiated m3 cancer with LVI. Both cancers were
not endoscopically manageable and it is probable that these patients would have been cured if they had undergone esophagectomy immediately after the first ER.

This study has also several limitations. First, this is a retrospective study in two tertiary referral centers for early AEC. Second, we can not completely exclude the presence of LNM in our patients. To detect LNM with a high certainty it is either necessary to perform esophagectomy with extensive lymph node dissection or, in case of endoscopic therapy, to follow-up the patients for a long period. In this study only 7 patients underwent esophagectomy after the ER and a median of 17 lymph nodes were detected in the resection specimens, a number that although acceptable does not exclude the possibility of sampling error. On the other hand, absence of LNM during a median of 33 months follow-up after surgery argues in favor of true absence of LNM in these patients. Still, the majority of our patients underwent endoscopic therapy and was therefore endoscopically followed. Given the relative short follow-up duration in these patients (median 26 months) in combination with the low sensitivity of EUS for detection of LNM (75-80%), we can not completely exclude the presence of LNM in these patients.35, 36 LNM may thus still become overt in the following years. Then again, a follow-up of 26 months may not be that short for LNM detection, since the majority of patients develop locoregional recurrences within 12 months after potentially curative surgery of AEC and in early AEC locoregional and distant metastasis are reported to occur after a mean of 16 months.16, 37 Another limitation of this study is the relatively small number of patients in the sm1 and sm2/3 categories, although most surgical series reporting on these subcategories also had a small number of patients in these subcategories. Finally, no evaluation could be performed of possible predictors for LNM such as tumor differentiation and LVI because no LNM were found. A poor differentiation of the tumor and presence of LVI have been reported to be associated with LNM in AEC.18, 19, 21 These two factors may thus be useful for the selection of patients with a higher risk of LNM.

In conclusion, this study shows no LNM for m3, sm1 and sm2/3 AEC assessed in ER specimens and therefore suggests that the risk of LNM is lower than assumed by surgical series. The current data suggest that the current guidelines to restrict endoscopic therapy to selected patients with mucosal cancers are valid as it comes to including m3 AEC and may also suggest that selected patients with submucosal cancers (sm1, well or moderately differentiated and no LVI) may be eligible for endoscopic management as well. Confirmation of these results is needed in larger series with longer follow-up.
References


Part II: Endoscopic therapy in Barrett’s esophagus


