Endoscopic Management of Barrett’s High-Grade Dysplasia and Early Stage Esophageal Cancer

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Introduction:

In recent years there has been intense interest in prevention and early curative treatment for esophageal adenocarcinoma (EAC). Several papers have been published describing the use of endoscopic mucosal resection and its positioning for use to treat early EAC arising from Barrett’s Esophagus (BE). There are approximately 10,000 new cases of EAC each year in the United States. This incidence of this disease is increasing. The 5 year survival for EAC is less than or equal to 15%.

Based out of an early experience using endoscopic therapy in patients with high grade dysplasia or early cancer in those who are unfit for esophagectomy, endoscopic mucosal resection combined with widespread ablative techniques for BE, became more fully developed and appreciated for their curative potential. As patients with early EAC were evaluated for consideration of EMR ± ablative therapy criteria were developed for determining safety and efficacy of EMR.

Limited submucosal invasion is an area of current controversy. European literature, which will be reviewed here, suggests it is safe to perform EMR on those with “low risk” T1sm1 lesions. This has not been adopted (in those who are definite surgical candidates) in the US.

This review will focus on several recent papers that investigate the role of endoscopic mucosal resection as staging histopathology to predict success or failure of local control of this potentially devastating disease.

Body:

The first article for discussion is “Early Barrett’s carcinoma with “low-risk” submucosal invasion: long-term results of endoscopic resection with a curative intent” published in the American Journal of Gastroenterology in 2008 by Manner H, May A, and Pech O and others out of Wiesbaden, Karlsruhe, and Bayreuth, Germany. This study describes a prospectively collected cohort of patients evaluated and treated over a 10 year period (1996-2006) with EAC with submucosal involvement.

Out of over 600 patient referred for BE and EAC related problems, eighty patients fulfilled criteria for EAC with submucosal involvement. These patients all were staged with a combination of EGD with biopsies then EMR, as well as EUS with FNA, Chest X-ray, abdominal ultrasound, and CT scan. They assessed at EGD the macroscopic type according to the Japanese Classification for early stomach cancer: “polypoid tumor (type 1), flat and slightly elevated (type 2a) flat and level (type 2b), flat and depressed (type 2c), and ulcerated (type 3)”

Criteria for inclusion for endoscopic management included the following. 1) No evidence of “or raised suspicion of” more advanced local tumor stage. This included 1) No EUS suspicion of invasion of SM2 or SM3 layers. 2) No type 3 tumors 3) No evidence of lymphadenopathy (FNA was used) 4) No evidence of metastatic disease 5) Low tumor differentiation.
There were 21 patients out of this initial 80 that met the criteria listed in the previous paragraph. These patients were deemed “low risk” for endoscopic management and underwent endoscopic mucosal resection, maximal acid suppression dose-titrated by 24 hour pH-metry, and had close follow up. Endoscopic mucosal resection was performed using either a cap system or a ligation device.

One of the 21 patients went directly to esophagectomy and is alive and well. Another died 3-4 years into follow up from a cerebral aneurysm. Another did not have complete control of tumor after 2 EMR sessions and was referred to surgery. The remaining 18/21 had CR after a mean follow up of 5.3 ± 6.5 months and a mean of 2.9 ± 2.7 EMR sessions. There was 66% 5-year survival in the original 21 that met low risk criteria. All deaths were non-EAC related. Metachronous early EAC lesions appeared in 27.8% of patients during a mean follow up of 61.9 ± 11.1. In all of these instances they were managed successfully with endoscopic therapy.

The next article for review is “Endoscopic resection for Barrett’s high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit.” Published in the American Journal of Gastroenterology in 2010 by Moss A, Bourke MJ, Hourigan LF et al out of academic institutions in Sydney and Brisbane Australia.

This study describes 75 prospectively enrolled patients with BE and high grade dysplasia (HGD) or early EAC. 5 of these patients were directly referred for EMR and the remaining 70 were evaluated initially at one of the main sites. Prior to EMR patients were staged with CT and/or EUS prior to 2005 after which only those with lesions suspicious for invasion (lesion> 2 cm, ulcerated or depressed lesions) were mandated to have pre EMR staging.

EMR was performed using a cap in the earlier years of enrollment, but later all were done using multi-band mucosectomy technique. EMR specimens were histopathological assessed for dysplasia and depth of invasion of EAC in the absence or presence of involved margins. These were compared to pre-EMR biopsies and esophagectomy specimens. All those in the study with short segment BE (<3-cm) underwent complete eradication of BE (CBE).

89% of those in this study had HGD and only 11% with early EAC. EMR was successful in 100% with a median specimen size of 1.4 cm with a mean of 3 EMR sessions per patient. Comparing EMR to jumbo biopsy evaluation resulted in a change of stage in 48%. 28% were down staged and 20% up staged. After the 1st EMR session 57% were felt to have clean margins (R0).

10 patients had mucosal EAC in an EMR specimen. These were successfully managed endoscopically. Seven patients had submucosal invasion and were therefore referred to surgery of which 3 had esophagectomy. The other 4 underwent endoscopic resection due to either refusing (2 patients) or not being surgically fit (2 patients). Two of these patients successfully underwent EMR and CBE. Two patients underwent radiotherapy. One continues follow up and the other died of radiation pneumonitis.

35 patients were eligible for CBE at follow up with a 94% success rate. In one patient who was CBE eligible further EMR demonstrated submucosal invasive EAC and esophagectomy was performed. Besides this patient none of the CBE-eligible patients developed metachronous lesions.

In mean follow up of 31 months, eight of the 35 non-CBE patients developed metachronous lesions (3 HGD, 5 EAC) and none were at previous EMR sites. 4 patients (1 HGD, 4 EAC) had repeat EMR 3 successfully one found to have submucosal involvement and referred to surgery. One of these patients did go to esophagectomy and the remaining 4 patients deferred any treatment due to advanced age and significant co-morbidities.

5-year survival was 89% without any deaths related to BE/EAC but one treatment related death (radiation) who was too sick for surgery.

The next article for review is “Stepwise radical endoscopic resection for the eradication of Barrett’s oesophagus with early neoplasia in a cohort of 169 patients” published in Gut 2010 by Pouw RE, Seewald S, Gondrie JJ et al. This was a retrospective analysis of patients who were treated with stepwise radical endoscopic resection at 4 European centers. Patients had to meet selection criteria of: 1) BE length ≤ 5 cm; 2) HGD or EAC on biopsies or previous EMR pathologic specimens; 3) No invasion
> TM1 Sm1, poorly/undifferentiated cancer (G3/G4), lymphovascular invasion, positive deep resection margins. 4) No signs of lymph node or distant metastasis on EUS or CT 5) other types of ablation already employed despite eligibility.

EMR is preformed by eradicating an index lesion if present using either a cap technique or multiband mucosectomy. This was done to index lesion and 50% of the circumference of the BE. Subsequent sessions were done 4-8 weeks (“stepwise radical endoscopic resection”) later using the same techniques but with the intent to resect the entire Barrett’s mucosa. Argon plasma coagulator was used to ablate bridges or islands between resected areas.

169 patients were eligible from January 200 to September 2006. Mean BE length of 3-cm, 127 had visible lesions, 88 patients had HGD and 54 EAC was worst histological grade at any point. 27 patients had no prior diagnosis of HGD or EAC prior to EMR after which they received one of these diagnoses.

ITT analysis of primary endpoints revealed no deaths, 5 patients withdrew from treatment for various reasons not related to treatment at all. Three patients were lost to follow up. 161/169 finished the protocol with complete eradication of neoplasia (CR-N) in 97.6%. IM was eradicated (CR-IM) in 89%. Other than those lost to follow up, one single patient despite having esophagectomy went on to have metastatic EAC and die. 7 patients had EMR showing T1sm1 as worst histology.

160 patients entered a follow up phase with a median time from start of treatment to the last EGD was 32 months. 10 patients were lost to follow up. CR for end of treatment and follow up phase was CR-N 95.3% and CR-IM 80.5%. 9 patients required re-treatment and all had CR-N. 2 patients did not achieve CR-IM.

5/169 patients underwent esophagectomy for non-endoscopically respectable lesions. One patient had T1sm1 but had no further evidence of disease at esophagectomy.

Complications included a 1.0% perforation rate (0.5% severe perforation) and 1.0% bleeding rate. 49% had stenosis requiring a median of 3 dilations or stent.

The final paper to be reviewed is “Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma published in Clinical Gastroenterology and Hepatology by Badreddine RJ, Prasad GA, Lewis JT, et al.

This was a retrospective review of the surgical pathology on 80 patients who underwent esophagectomy for HGD/EAC between 1997-2007. Unlike the previous studies, EMR was not used to assess these tumors. Tumors that were invading muscularis propria and intra-mucosal tumors were excluded. Any patient who had neoadjuvant or radiation treatment was excluded. Pre-operative staging was assessed. Tumors were categorized as stage T1sm1 or T1sm2/3.

31 tumors were T1sm1 and 49 were T1sm2/3. Of those tumors with T1sm1 stage 12.9% had associated LN metastases, whereas of those stage T1sm2/3 20% had LN metastases. There was no statistically significant difference between these groups. Tumors with T1sm1 stage had lymphovascular invasion in 32% and those with T1sm2/3 had it in 35% also showing no significant difference. Recurrent cancer occurred in 9.6% of T1sm1 disease and 8.2% of T1sm2/3. There were identical 5 year overall and cancer free survival comparing T1sm1 to sm2/3 groups.

Median survival was 46.5 months for all patients with cumulative mortality of 39% during follow up. Median survival for T1sm1 was 52 months vs. 35.5 months in the T1sm2/3 group. Of those who died n the T1sm1 group 3 (9.6%) died of recurrence and 2 (6.4%) died due to complications of surgery. In the T1sm2/3 group 5 (10%) died of recurrent disease and 5 (10%) died of post-op complications. Predictors of death were age at esophagectomy and recurrence of cancer. Other factors were not significant in predicting survival.

**Conclusion:**

EMR is now a procedure of choice in approaching early EAC that is not locally advanced. EMR is a useful staging tool to determine the right treatment approach, while assessing ability to completely resect an index lesion. Although controversial many would recommend surgery to patients, who are good surgical candidates,
with EAC and any degree of submucosal involvement, while recommending EMR (+/- adjuvant chemo or radiation therapy) and close follow-up for elderly patients with co-morbidities. However this field is evolving and there are not enough patients with limited submucosal involvement to comment on a preferred course of action.

Even though esophagectomy itself confers 2-5% mortality in these patients in a high volume center PMID 21532466, the risk of lymph node involvement, lymphovascular invasion and death from recurrence is higher in those with SM-1 invasion (15-20%). PMID EMR carries a very low mortality with 0% at 90 days. PMID 21532466 Although the morbidity of esophagectomy is an issue that must be weighed into this equation for each patient.

These studies do reveal a wealth of experience using EMR in treating mainly HGD and some very early EAC. The addition of complete eradication of Barrett’s is probably a very important one as the rate of metachronous lesions is quite high in those who have significant amounts of remaining BE. How to ablate Barrett’s in the safest most efficient and effective manner is still unclear.

Stepwise radical endoscopic resection has a significant complication rate but is highly effective in the hands of those in the study reviewed here. Radiofrequency ablation is an attractive way to ablate BE. More data concerning its use with EMR in early EAC at long term follow up published in peer review journals is eagerly awaited.

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References:


