Risk of recurrence of Barrett's esophagus after successful endoscopic therapy CME

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Background and Aims: Previous estimates of incidence of intestinal metaplasia (IM) recurrence after achieving complete remission of IM (CRIM) through endoscopic therapy of Barrett's esophagus (BE) have varied widely. We performed a systematic review and meta-analysis of studies to estimate an accurate recurrence risk after CRIM.

Methods: We performed a systematic search of multiple literature databases through June 2015 to identify studies reporting long-term follow-up after achieving CRIM through endoscopic therapy. Pooled incidence rate (IR) of recurrent IM, dysplastic BE, and high-grade dysplasia (HGD)/esophageal adenocarcinoma (EAC) per person-year of follow-up after CRIM was estimated. Factors associated with recurrence were also assessed.

Results: We identified 41 studies that reported 795 cases of recurrence in 4443 patients over 10,427 patient-years of follow-up. This included 21 radiofrequency ablation studies that reported 603 cases of IM recurrence in 3186 patients over 5741 patient-years of follow-up. Pooled IRs of recurrent IM, dysplastic BE, and HGD/EAC after radiofrequency ablation were 9.5% (95% CI, 6.7-12.3), 2.0% (95% CI, 1.3-2.7), and 1.2% (95% CI, .8-1.6) per patient-year, respectively. When all endoscopic modalities were included, pooled IRs of recurrent IM, dysplastic BE, and HGD/EAC were 7.1% (95% CI, 5.6-8.6), 1.3% (95% CI, .8-1.7), and .8% (95% CI, .5-1.1) per patient-year, respectively. Substantial heterogeneity was noted. Increasing age and BE length were predictive of recurrence; 97% of recurrences were treated endoscopically.

Conclusions: The incidence of recurrence after achieving CRIM through endoscopic therapy was substantial. A small minority of recurrences were dysplastic BE and HGD/EAC. Hence, continued surveillance after CRIM is imperative. Additional studies with long-term follow-up are needed. (Gastrointest Endosc 2016;83:1090-106.)

Endoscopic therapy is currently the accepted first-line treatment modality for Barrett's esophagus (BE)-related dysplasia and mucosal adenocarcinoma.[1,2] Several endoscopic modalities are used in isolation or in combination for endoscopic therapy of BE, such as EMR, radiofrequency ablation (RFA), photodynamic therapy (PDT), cryotherapy, argon plasma coagulation (APC), multipolar electrocoagulation, and laser therapy.[3] Endoscopic therapy with EMR followed by PDT or RFA has been shown to be effective in reducing the risk of progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC).[4-6]

High rates of elimination of intestinal metaplasia (IM) and dysplasia have been shown in several reports from single and multicenter studies with short- and medium-term follow-up.[7,8] As the benefits of initial ablative therapy are well described, attention is now focused on the durability of response to endoscopic therapy, specifically recurrence rates of IM, dysplasia, and carcinoma. Studies have varied considerably in estimates of recurrence of IM after achieving successful ablation defined as complete remission of IM (CRIM). Although some studies have reported low rates of recurrence,[9-11] others have reported significantly higher rates of recurrence.[12] The wide variation between studies could be because of several factors, both implicit (patient characteristics such as age, smoking status, use of potentially chemopreventive medications after CRIM) and explicit

Abbreviations: APC, argon plasma coagulation; BE, Barrett's esophagus; CRIM, complete remission of intestinal metaplasia; DBE, dysplastic Barrett's esophagus; EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction; HGD, high-grade dysplasia; IM, intestinal metaplasia; IR, incidence rate; NDBE, nondysplastic Barrett's esophagus; PDT, photodynamic therapy; RFA, radiofrequency ablation.

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(footnotes continued on last page of article)

(differences in study design, follow-up duration, and surveillance protocols after CRIM). Several potential predictors of recurrence have been assessed, but only in small studies with limited power to make conclusive observations.[13-15]

It is important to reliably estimate the recurrence risk after successfully achieving CRIM for several reasons. First, recurrent dysplastic BE (DBE) or carcinoma is important to detect, because it may require further endoscopic therapy or esophagectomy. Second, currently, there are no consensus/guidelines on duration of follow-up and frequency of surveillance endoscopies after successfully achieving CRIM, and accurate estimates of recurrence would be helpful in determining this. Finally, the cost-effectiveness of endoscopic therapy for BE will depend on durability of CRIM and need for additional therapy of recurrent BE.

We performed a systematic review and meta-analysis of all studies that reported long-term results after achieving CRIM in BE patients using endoscopic eradication therapy to estimate an accurate recurrence risk (for IM and dysplasia). Although some techniques like PDT and APC are not currently in use, we believed it was important to include them in this review given their pioneering role in demonstrating success with endoscopic therapy and because other than RFA, level 1 evidence supporting endoscopic therapy for BE is only available for PDT.[6] Also, outcomes with older modalities can serve as a useful comparator for current modalities. We also identified clinical factors associated with recurrence of IM after CRIM.

METHODS

This systematic review was performed according to guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions.[16] It is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[17] We followed a priori established protocol.

Search strategy

We conducted a systematic literature search of several databases from each database's inception to June 1, 2015 for relevant articles on recurrence of IM, dysplasia, or adenocarcinoma after endoscopic treatment of DBE and nondysplastic BE (NDBE). The databases included MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. The search was restricted to the studies on human participants published in English. The search was conducted by an experienced librarian with input from the study authors (R.K., S.S., and P.G.I.). The details of the search strategy and data sources are reported in Appendix 1 (available online at www.giejournal.org).

Selection criteria

We included studies that met the following inclusion criteria: (1) reported recurrence of IM, dysplasia, and/or EAC in BE subjects (dysplastic and nondysplastic) who achieved CRIM using any endoscopic therapy and (2) reported follow-up period since CRIM in "patient-years" or reported mean/median follow-up period after CRIM and number of patients in surveillance, thereby permitting calculation of follow-up period since CRIM in "patient-years." Recurrence was defined as the presence of IM in the esophagus and/or gastroesophageal junction (GEJ) after achieving CRIM. CRIM was defined by individual studies as biopsy samples being negative for IM on a single or 2 successive endoscopies.[12,18-20] We included all endoscopic therapeutic modalities. We excluded studies that used >1 endoscopic ablation modality, studies with mean/median follow-up < 1 year after CRIM was achieved, studies with <20 subjects who achieved CRIM, studies that reported recurrence after complete remission of dysplasia instead of CRIM, studies with subjects who had previously failed endoscopic therapy, and case-control studies, letters to the editor, editorials, and review articles. Studies using a combination of 1 endoscopic ablative modality with EMR were included. When multiple publications from the same population were identified, only data from the most recent comprehensive report were included. Two of the included studies had 2 arms, 1 comparing outcomes with different endoscopic modality[21] and 1 comparing outcomes in long- versus ultralong-segment BE.[22] For the purpose of the review, each arm was counted as a separate study.

Data abstraction and quality assessment

After identifying relevant studies, data on study characteristics, patient characteristics, treatment characteristics, study outcomes, and risk factors for recurrence were abstracted onto a standardized form by 2 authors (R.K., K.R.). Details of data abstraction are reported in Appendix 2 (available online at www.giejournal.org).

The quality of the individual studies was independently assessed by 2 authors (RK, KR) using a scale modified from the Newcastle-Ottawa scale for cohort studies.[23] This quality score consisted of 10 questions. The details of the quality scale are reported in Appendix 3 (available online at www.giejournal.org). A score of $\geq$7, 4 to 6.5, and <4 was considered suggestive of a high-, medium-, and low-quality study, respectively.

Outcomes assessed

The primary outcome of the review was to assess the annual incidence rate (IR) of IM recurrence after achieving CRIM using RFA given that it is the most commonly used endoscopic modality in current practice. Secondary outcomes measured included annual IR of IM recurrence after use of all endoscopic modalities and IR of recurrent DBE and HGD/EAC.

We performed preplanned subgroup analysis based on primary endoscopic modality (eg, RFA, PDT, APC), study location (eg, North America, Europe), baseline dysplasia status in pretreatment histology (NDBE vs DBE $\pm$ early