Use of enteroscopy for the detection of malignant and premalignant lesions of the small bowel in complicated celiac disease: a meta-analysis

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Background and Aims: Enteroscopy (wireless or wired) is the reference standard for small-bowel (SB) diseases, and it has been applied to detect SB malignancies in complicated celiac disease (CD) with heterogeneous results. The aim of this meta-analysis was to obtain a diagnostic yield (DY) by pooling the data of studies that investigated the use of enteroscopy to detect SB adverse events in CD.

Methods: We performed an online search for studies estimating the DY of wireless and wired enteroscopy in predicting the presence of SB premalignant and/or malignant lesions. The DerSimonian and Laird random-effects method was used to pool the arcsine-transformed proportions of patients with the events. Three meta-analyses were performed considering the following events: the presence of a malignancy, premalignant damage (ulcerative jejunoileitis [UJ]), or the presence of a malignancy or UJ. A subgroup analysis was performed after extracting (if possible) patients with refractory CD (RCD).

Results: Of the 529 titles initially resulting from the search, 10 studies on capsule enteroscopy (CE) and 3 on double-balloon or push enteroscopy met the inclusion criteria. Overall, 439 and 76 patients were enrolled in these studies using CE and enteroscopy, respectively. Twelve tumors and 47 UJs were found by CE versus 8 tumors and 13 UJs detected by wired enteroscopy. For malignancies the CE yield was 1.9% (95% CI, .5%-3.8%) and wired enteroscopy yield 8.7% (95% CI, 0%-21.2%); similarly, for UJ the DYs were 8.4% (95% CI, 2.1%-17.7%) and 16.7% (95% CI, 8.7%-26.3%); for either UJ or neoplasia the DYs were 13.0% (95% CI, 5.6%-22.5%) and 27.7% (95% CI, 14.8%-42.6%). For RCD the DYs of all enteroscopic techniques were 1.8% (95% CI, 0%-7.7%) for neoplasia, 22.3% (95% CI, 8.2%-39.7%) for UJ, and 27.5% (95% CI, 13.1%-44.2%) for either.

Conclusions: Enteroscopy is a powerful and efficient diagnostic tool for the detection of SB malignancies in complicated CD. (Gastrointest Endosc 2017;86:264-73.)

Celiac disease (CD) is the most common autoimmune enteropathy in Western countries, with an estimated prevalence ranging from 1:100 to 1:200.[1] CD is characterized by an heterogeneous clinical picture, including intestinal and extraintestinal symptoms, and is diagnosed in the presence of serum autoantibodies (antitransglutaminase type 2 IgA), duodenal villous atrophy, and a specific genetic background, which corresponds to the HLA DQ2 and/or DQ8 haplotypes.[2] A gluten-free diet (GFD) usually leads to clinical, serologic, and histologic remission, making CD a disorder with a benign prognosis.[3] However, CD can be, infrequently, complicated by the development of premalignant mucosal lesions, such as ulcerative jejunoileitis (UJ), which is accompanied by molecular alterations of T lymphocytes, or malignancies of the GI tract, namely enteropathy-associated T-cell

Abbreviations: CD, celiac disease; CE, capsule enteroscopy; DAE, device-assisted enteroscopy; DBE, double-balloon enteroscopy; DY, diagnostic yield; EATL, enteropathy-associated T-cell lymphoma; GFD, gluten free diet; RCD, refractory celiac disease; SB, small bowel; TCR, T-cell receptor; UJ, ulcerative jejunoileitis.

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lymphoma (EATL) and adenocarcinoma of the small bowel (SB).[4] The occurrence of such adverse events is more frequent when dealing with a refractory CD (RCD) type I or II. Several studies have estimated a relative risk for neoplastic intestinal adverse events in CD, ranging from 2 to 40 for primary gut lymphoma and from 10 to 60 for SB adenocarcinoma, whereas the development of a GFD refractory state is usually less than 1% of CD cases.[5,6]

Although uncommon, the aforementioned premalignant lesions and malignancies are characterized by poor prognosis, as indicated by an overall survival rate at 30 months of 58% and 45% of patients with SB adenocarcinoma and lymphoma, respectively.[7] Different factors are involved in the development of tumors in CD: age at CD diagnosis,[8] poor mucosal healing in spite of an ongoing GFD,[7] and presence of an RCD.[4] However, the main factor worsening the mortality rate of these tumors is diagnostic delay, which often reduces the therapeutic options available to affected patients.

Until recently, the difficulty of exploring the SB was the major problem for early diagnosis of tumors originating from the SB mucosal layer. In the last decade, the introduction of SB capsule enteroscopy (CE, wireless enteroscopy) and device-assisted enteroscopy (DAE, wired enteroscopy) has greatly improved the diagnostic workup of the SB mucosa.[9] CE has been applied to both the diagnosis of CD and the management of CD patients with a complicated course to detect or exclude the presence of any SB malignancies. However, little data are available on the use of DAE (probably because of its invasive nature and potential side effects).[10] Unfortunately, the findings currently available, mainly obtained from retrospective studies, are heterogeneous and difficult to interpret.[11-23]

Even if the usefulness of enteroscopy to diagnose CD is extremely limited if not null, the application of it in detecting SB malignancies can support a timely diagnosis and improve the prognosis of CD patients affected by these severe adverse events.[10] Based on these considerations, this meta-analysis aimed to evaluate the diagnostic yield (DY) of enteroscopy for SB malignancies and preneoplastic lesions, such as UJ, for patients with CD.

METHODS

Protocol and criteria applied

The Preferred Reporting System for Systematic Reviews and Meta-Analyses was used as a guideline. The inclusion criteria for article types were prospective or retrospective, observational or comparative studies in which enteroscopic techniques were performed with the intention to detect any possible adverse event in CD patients with a complicated course. Case reports, congress reports, commentaries, editorials, and review articles were excluded from the analysis. Also, any study planned for the diagnosis of CD but not aimed at the detection of potentially harmful adverse events of CD were excluded.

Literature search and selection of studies

A comprehensive literature search was carried out to identify peer-reviewed articles on enteroscopy and CD published up to December 2016. The PubMed database, EMBASE, Web of Science, and the Cochrane Library were systematically searched using 2 search strategies, 1 for wireless enteroscopy (CE) and the other for wired enteroscopy. In addition, a manual search was also carried out through the bibliographies of the identified articles.

The CE search strategy for PubMed was as follows: *("capsule endoscopy"[MeSH Terms] OR ("capsule"[All Fields] AND "endoscopy"[All Fields]) OR "capsule endoscopy"[All Fields]) AND ("coeliac disease"[All Fields] OR "celiac disease"[MeSH Terms] OR ("celiac"[All Fields] AND "disease"[All Fields]) OR "celiac disease"[All Fields]).* The wired enteroscopy search strategy was as follows: *("Balloon Enteroscopy" or "Double-Balloon Enteroscopy"[MeSH Terms] OR ("enteroscopy"[All Fields] AND "endoscopy"[All Fields]) OR "enteroscopy"[All Fields]) AND ("coeliac disease"[All Fields] OR "celiac disease"[MeSH Terms] OR ("celiac"[All Fields] AND "disease"[All Fields]) OR "celiac disease"[All Fields]).*

Three investigators (L.E., M.L., and F.B.) independently searched through titles and abstracts to identify studies potentially pertinent. During the titles screening stage, any article with a title not related to CD and enteroscopy was excluded. During the abstract review stage, any article not matching the inclusion criteria was excluded. In case of any discordance between the aforementioned reviewers, the conflict was resolved by referral to 2 other authors (M.F. and G.C.).

After completing the selection of studies, 3 authors (L.E., M.L., and F.B.) extracted the data from each study and input them into a standard Excel spreadsheet (Microsoft Corporation, Redmond, Wash). The data retrieved were as follow: first author, year of publication, study design, number of patients, patient demographics, type of enteroscopy, diagnosis of malignant or premalignant SB lesions, and DY. Whenever possible, patients with RCD were extracted for further analysis. In particular, the DY was defined as the ratio between the number of events (UJ alone, neoplasia alone, and the combined 2) and the number of patients included in each study.

Data analysis

A graphical descriptive representation of the included studies was performed by using forest plots. For the primary studies, 95% confidence intervals (CIs) were calculated with the binomial exact method. Because a high degree of clinical heterogeneity among studies was expected, the meta-analysis of the DY was performed using a random-effects model for proportions (DY) with the DerSimonian and Laird method. All meta-analyses were carried