Peer Review File

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Reviewer A

Major points:

Comment 1: The authors stated that progression to EAC occurred in 0.14% per patient-year (95% CI, 0.00%-0.55%) after eradication and in 0.30% per patient-year (95%CI, 0.21%-0.39%) after surveillance-only. However, as the authors stated, progression rates after surveillance-only were referred from a previous systematic review on EAC incidence in NDBE (reference 3). Therefore, it is difficult to say that eradication therapy is better than surveillance-only based on this study.

Reply 1: The most reliable method to determine whether eradication or surveillance-only should be preferred to prevent EAC would be to combine data from RCTs, in which the two management strategies are directly compared. Only 2 RCTs that compared eradication with surveillance-only for NDBE reported on EAC incidence. No cases of EAC were identified in either intervention groups in both studies, likely due to small sample sizes (40 and 55) and relatively short follow-up time (1-6 years). The relative risk ratio calculation we intended was therefore not possible. To allow for an indirect comparison, we therefore analyzed progression rates reported in a previous systematic review on EAC incidence in NDBE after surveillance-only as commented above.

The reviewer is correct in that superiority of eradication therapy over a surveillance-only strategy is difficult to assess. Based on the indirect comparison with EAC incidence after surveillance-only, we concluded in the Discussion that a beneficial outcome following eradication of NDBE is questionable. We thus recommended against eradication therapy in a large population of NDBE patients of whom most will never progress to EAC.

Comment 2: As the authors stated, several guidelines advise against eradicating NDBE because of its low risk of progression to EAC. In fact, pooled annual cumulative incidence of EAC was 0.3% per patient-year even after surveillance-only (reference 3). Previous study (reference 14) have already shown that annual cumulative incidence of EAC post-eradication was 0.16% which suggests that the effectiveness of eradication therapy is small. It is not clear why the authors intended to examine the efficacy, durability and safety of endoscopic eradication therapy for NDBE again.

Reply 2: The previous meta-analysis on cumulative incidence of EAC post-eradication (reference 15 in the revised manuscript) included studies op to 2008. It was considered likely that new research on eradication of NDBE may had been published in the 13 years after publication of aforementioned meta-analysis. Furthermore, several publications on new methods to screen for BE and early EAC have been published over de last decade. Implementation of such screening strategies may potentially have a burden our healthcare systems with a large volume of NDBE patients, especially when all NDBE patients are enrolled in surveillance programs. Review of strategies to manage NDBE is therefore highly warranted. A recent paper by Graham et al., (1) proposed a new paradigm, i.e., to improve BE prevention, to systematically screen for BE, to eradicate all identified BE (including NDBE) along with aggressive acid-suppressive anti-reflux therapy and to limit surveillance practices. Benefit and risk of proposed strategies for NDBE management like these and other should be carefully evaluated. We hypothesized that it may well be possible that new research was published using innovative techniques that were not available before 2008 to eradicate NDBE. We therefore conducted this systematic review including studies up to 2020.

Additionally, efficacy, durability and most importantly safety were never evaluated systematically for NDBE specifically. The pooled data in this meta-analysis may help clinicians and patients to better weigh benefits and risk in daily practice.

Comment 3: EAC was found in 4 of 928 NDBE patients treated with endoscopic eradication therapy. The authors stated that the pooled annual cumulative incidence of EAC post-eradication was 0.14%. However, follow-up period is different in each studies.

Reply 3: The reviewer is correct in that follow-up periods were different in various studies. We calculated an annual cumulative incidence rate before pooling the data to correct for different follow-up times. The cumulative incidence of EAC post-eradication was 0.14% per year. Another question might be whether a patient with BE continues to have the same risk of developing EAC over the years. The risk could either be linear over time or reach a plateau at a certain moment. The relatively short follow-up time in most included studies in this meta-analysis precludes from estimating the trend in EAC risk after eradication therapy over the years, which we acknowledge as a limitation of this meta-analysis.

Minor points:

Comment 1: Better to have native English editing.

Reply 1: The manuscript has been corrected by someone fluent in English.

Comment 2: The authors included studies with at least 15 NDBE patients who were treated using any form of EET to eradicate NDBE. It is not clear a reason that studies with at least 15 patients were included.

Reply 2: The Authors have modified the text in the Methods section, line 94, 103-104. We added that studies containing fewer than 15 NDBE patients were excluded, because studies with minimal weight will unlikely impact pooled effect sizes in meta-analyses

Reviewer B

Comment 1: Overall excellent systematic review and meta-analysis that helps inform current practice patterns of treatment of BE.

Reviewer C

Comment 1: Abstract Background: add statement about the goal of study was to complete a systematic review.

Reply 1: The Authors have modified the Abstract Background, line 19. We have added that the goal of the study was to complete a systematic review.

Comment 2: Why only one PDT study? I believe more should have been captured.

Reply 2: We provide a detailed description of identified PDT studies and reasons for exclusion of these studies in the table below.

PDT studies identified through systematic search and citation searching	Included/excluded	Reason for exclusion
Kelty et al., 2004 (2)	Included	
Overholt et al., 1995 (3)	Excluded	< 15 NDBE
Overholt et al., 1999 (4)	Excluded	Only patients with BE-related neoplasia included
Ackroyd et al., 2000 (5)	Excluded	Only patients with BE-related dysplasia included
Ortner et al., 2002 (6)	Excluded	< 15 NDBE
Hur et al., 2003 (7)	Excluded	No outcome of interest (cost-effectiveness analysis)
Hage et al., 2004 (8)	Excluded	Outcome not separable for NDBE and BE with LGD
Kelty et al., 2004 (9)	Excluded	FU < 12 mo
Vij et al., 2004 (10)	Excluded	No outcome of interest (cost-effectiveness analysis)
Hage et al., 2005 (11)	Excluded	Outcome not separable for NDBE and BE with LGD
Overholt et al., 2005 (12)	Excluded	Only patients with BE-related neoplasia included
Ragunath et al., 2005 (13)	Excluded	Only patients with BE-related neoplasia included
Hage et al., 2006 (14)	Excluded	< 15 NDBE
Comay et al., 2007 (15)	Excluded	No outcome of interest (cost-effectiveness analysis)
Overholt et al., 2007 (16)	Excluded	Only patients with BE-related neoplasia included
Badreddine et al., 2010 (17)	Excluded	< 15 NDBE

Comment 3: Introduction: add reference after sentence about high costs (page 1 of Intro).

Reply 3: A reference to the issue of high costs has been added to the manuscript (reference 11 in the revised manuscript).

Comment 4.a: Shouldn't PDT be in list of keywords?

Reply 4.a: Photodynamic therapy has been has added to the list of keywords in the methods section (line 85) as the search term "photodynamics" was indeed included in all search strategies (supplementary file 1).

Comment 4.b: Add that the reviewers of abstracts had no COI.

Reply 4.b: The Authors have added a COI statement to the paragraph elaborating on title/abstract review, line 91.

Comment 5: Under adverse events: add comment/breakdown of which modalities had strictures, etc. It is in Table but should be in Results.

Reply 5: The authors have modified the text in Results, line 224-228. We have added the pooled proportions of occurrence of strictures, bleedings and perforations after eradication for NDBE, stratified per treatment modality.

Comment 6.a: Add ref for sentence with "...costly and burdensome."

Reply 6.a: Reference to this topic has been added to the manuscript (reference 11 in the revised manuscript).

Comment 6.b: For economic analysis, please add sentence or two substantiating that this cost is "...too high for society..." Compare with QALY gained for screening interventions (e.g., colonoscopy or mammography).

Reply 6.b: We agree that it does not seem entirely appropriate to compare costs per QALY gained for a treatment intervention versus a screening intervention. Models for screening and treatment interventions compare competing strategies at a different level. Cost-benefit analyses of screening interventions incorporate downstream surveillance and treatment costs in a screening strategy scenario which is subsequently compared with a no screening scenario.

A better parallel might be a cost-benefit analysis comparing polypectomy of non-dysplastic polyps at colonoscopy (also a therapeutic intervention for a premalignant disease aimed to prevent cancer development) vs surveillance of these polyps. However, such cost-benefit study has not been conducted, likely because visible polyps are routinely resected in total during initial colonoscopy (with afterward pathological evaluation).

We have modified the text in the Discussion, in line 327.

Comment 6.c: It appears from Tables 1 and 2, that really APC and "laser" were associated with adverse events, so this needs to be expanded in Discussion as other modalities likely will provide benefit to NDBE patients.

Reply 6.c: The Authors have modified the Discussion, line 298-312. We have added that occurrence of EAC after EET for NDBE was only reported in studies using APC and laser therapy, but not after the currently most commonly used technique RFA. We also added that severe adverse events occurred most frequently in APC studies. We conclude that whether RFA is more effective and safe in treating NDBE than delineated in this meta-analysis of all methods combined remains undetermined.

Comment 6.d: elaborate more on need for risk stratification model.

Reply 6.d: The Authors have modified the Discussion, line 329-344. We agree with the reviewer that a risk stratification model is essential in the management of NDBE. Surveillance of NDBE might be leading to escalated use of financial and medical resources potentially without substantial benefit. A personalized approach through risk stratification of NDBE may lead to a more rational application of endoscopic surveillance and the use of EET for those most likely to progress to EAC. Current risk models might be supplemented with biomarker components and should be externally validated in population-based studies.

References

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