Total endoscopic eradication of Barrett’s esophagus: Study methodology, candidate selection, and clinical outcomes

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Introduction

This issue of *Endoscopy* focuses on total endoscopic eradication of Barrett’s esophagus, a condition described by the Australian surgeon Norman Rupert Barrett in 1950 [1]. This paper considers methodological aspects of studies of ablative therapies for Barrett’s esophagus, and how the choices made by investigators with respect to study methodology and candidate selection might impact the clinical outcomes observed in these studies.

The impact of study methodology on ablation trials

Defining Barrett’s esophagus

One very fundamental, and surprisingly unsettled, question regarding the conduct of clinical trials in Barrett’s esophagus is disease definition. Despite considerable advances in endoscopic technologies, authorities still cannot agree on the diagnostic criteria for Barrett’s esophagus. Although virtually all authorities agree with the concept that Barrett’s esophagus involves a metaplastic columnar epithelium replacing the normal squamous lining of the distal esophagus, this definition does not translate readily into practical diagnostic criteria for two reasons: (i) there are no universally accepted landmarks for delimiting the distal extent of the esophagus (i.e. for how to identify the gastroesophageal junction [GEJ]); and (ii) there is no clear consensus on the type of columnar epithelium required to establish the diagnosis of Barrett’s esophagus. We will consider each of these issues separately.

Identification of the gastroesophageal junction (GEJ)

Western endoscopists generally identify the GEJ as the proximal extent of the gastric folds when the esophagus and stomach are partially distended. This landmark was based on endoscopic observations in a study of only four individuals who were identified as normal because they had “no clinical evidence of esophageal disease” [2]. Three of the four individuals had hiatal hernias, furthermore, and one had endoscopic evidence of reflux esophagitis. Thus, the choice of the gastric folds as a marker for the GEJ is largely arbitrary, and its scientific basis is weak.

Endoscopists in Asia often have used the distal extent of the esophageal palisade vessels as their landmark for the GEJ [3]. The palisade vessels are a group of fine longitudinal veins located in the lamina propria of the distal esophagus ([Fig. 1](#Fig1)) [4]. The palisade vessels can be difficult to visualize by conventional endoscopic techniques, especially if the distal esophagus is inflamed. Even in autopsy studies in which the esophageal blood vessels are injected with resins that provide exquisite detail of the venous structures, it can be difficult to identify precisely the termination of the palisade vessels. Conceptually, furthermore, it is not clear why the distal end of the palisade vessels should be considered to be the end of the esophagus. Thus, as with the gastric folds criterion, the choice of the palisade vessels as a marker for the GEJ is arbitrary for the most part, with a fragile scientific basis.

Few studies have addressed specifically the problem of endoscopic location of the GEJ and, even in those that have done so, the accuracy of the criteria employed cannot be assessed meaningfully in the absence of a gold standard. It is not clear which is the best diagnostic criterion for the GEJ, and the reproducibility of the various proposed criteria have not been established by formal investigation. It is clear, however, that the landmarks do not always agree with one another. For example, the palisade vessels often can be seen to extend beyond the proximal margins of the gastric folds. Considering that a large majority of...
published studies on Barrett’s esophagus conducted over the past 20 years have used the gastric folds as the landmark for
the GEJ and, unlike the palisade vessels, the folds are not readily
obscured by esophageal inflammation, we suggest that investi-
gators continue to use the gastric fold landmark despite its
shortcomings.

**Type of columnar epithelium required for a diagnosis of
Barrett’s esophagus**

In 1976, Paull and his colleagues reported a pivotal study of 11
patients with Barrett’s esophagus who had esophageal biopsies
taken proximally to the lower esophageal sphincter under
manometric guidance [5]. Those investigators identified three
types of columnar epithelia in Barrett’s esophagus: (ii) a gastric
fundic-type epithelium that contained mucus-secreting cells,
parietal cells and chief cells; (ii) a junctional (also known as car-
diac-type) epithelium comprised almost exclusively of mucus-
secreting cells; and (iii) an intestinal-type epithelium (called
specialized columnar epithelium or specialized intestinal meta-
plasia) that contained prominent goblet cells. The gastric fundic-
and cardiac-type epithelia could be indistinguishable from the
normal gastric epithelium, and were thought therefore to have
little potential for malignant transformation. The intestinal-
type epithelium, in contrast, was clearly abnormal in its location,
and a number of studies suggested that this specialized intesti-
nal metaplasia was the epithelial type that was predisposed to
malignancy. Consequently, a practice evolved of requiring the
presence of intestinal metaplasia to establish a diagnosis of Bar-
rett’s esophagus [6].

In the late 1990 s, Chandrasoma challenged traditional dogma by
proposing that cardiac-type epithelium is not normal, but rather
a metaplastic epithelium that develops as a consequence of
chronic gastroesophageal reflux disease (GERD) [7]. According
to this hypothesis, the first step in esophageal metaplasia is a
change from squamous to cardiac epithelium, which later devel-
ops into intestinal metaplasia. Evidence that cardiac epithelium
can be metaplastic comes from studies of patients who have had
esophagectomy with esophagogastrectomy. This operation often
results in GERD in the esophageal remnant, followed by the de-
velopment of columnar metaplasia, which is initially cardiac in
type [8]. Furthermore, a recent study of 141 patients who had
endoscopic mucosal resection (EMR) for small esophageal ade-
nocarcinomas found that 71 % had cardiac epithelium, not intesti-
nal metaplasia, adjacent to the cancer, and that in 57 % no intesti-
nal metaplasia whatsoever was found in the EMR specimen [9].
These reports suggest that cardiac epithelium is metaplastic and
also has malignant potential.

In 2006, the British Society of Gastroenterology defined Barrett’s
esophagus as, “an endoscopically apparent area above the oeso-
phagogastric junction that is suggestive of Barrett’s which is
supported by the finding of columnar lined oesophagus on his-
tology. The presence of areas of intestinal metaplasia (IM), al-
though often present, is not a requirement for diagnosis” [10].
Clearly, this definition might include patients who have cardiac
epithelium in the esophagus and, conceptually, there is justifica-
tion for that inclusion. However, the inclusion of patients with
esophageal cardiac epithelium under the rubric of “Barrett’s esophagus” would substantially increase the number of patients
with the disorder. Furthermore, most studies on the risk of can-
cer in Barrett’s esophagus have included patients with intestinal
metaplasia either primarily or exclusively [11], and so the risk of
cancer for patients with cardiac epithelium is not clear. Quanti-
fication of cancer risk is needed to make rational decisions re-
garding the utility of eradication techniques for Barrett’s esoph-
agus.

The debate about whether patients with cardiac epithelium in
the esophagus have Barrett’s esophagus is primarily a semantic
issue. The key clinical question for patients who have cardiac
epithelium (without intestinal metaplasia) in the esophagus is:
What is the risk of developing esophageal cancer? As long as
that risk remains unclear, it is not possible to make meaningful
recommendations regarding the utility of eradication tech-
niques. Therefore, pending further data on this issue, we recom-
end that investigators limit their studies on eradication tech-
niques to patients who have intestinal metaplasia in the esoph-
agus.

**Spontaneous regression, sampling error, histological variability, and overestimation of effect in observational studies**

Observational studies of ablation in Barrett’s esophagus suffer
from multiple biases, which, taken collectively, may serve to ex-
aggerate the benefit derived from the techniques. Because these
studies generally lack a concurrent control group, it is important
to consider how inherent limitations of observational studies,
along with deficiencies in our technical abilities to assess Bar-
rett’s esophagus, impact the results of ablation trials.

To assess response to therapy after ablation, we perform random
sampling of mucosa to assess for dysplasia and metaplasia [12].
Unfortunately, it is well-described that dysplasia and metaplasia
occur in a patchy pattern throughout columnar-appearing mu-
cosa [13]. In fact, in as many as 66 % of individuals with Barrett’s
esophagus and low grade dysplasia, repeat biopsy does not de-
monstrate dysplasia [14]. Whether the lack of dysplasia on fol-
low-up biopsy represents sampling error, or whether this dys-
plasia has truly regressed, is unclear, but ex vivo examination of
dysplastic Barrett’s esophagus suggests that disease in at least
some patients is downgraded secondarily to sampling error [15].
Additionally, variability in the histological interpretation of en-
doscopic biopsies by pathologists will inevitably lead to down-
grading of some lesions [16,17]. Since many ablation trials re-
For patients who have Barrett's esophagus without dysplasia, the risk of cancer development is substantially higher than that of patients with dysplasia. The combination of these factors makes it reasonable to assume that 50% of that 80% effect would have occurred independently of any effect of the ablation, due to shortcomings in study methodology.

Selecting candidates for ablation trials

Barrett's esophagus without dysplasia

Barrett's esophagus per se causes no symptoms, and the condition has clinical importance only because it predisposes to esophageal adenocarcinoma. The only reasonable justification for eradicating Barrett's epithelium, therefore, is to prevent this lethal malignancy. Reasonable candidates for endoscopic eradication are those patients for whom the risk of developing esophageal cancer exceeds the risk of the endoscopic eradication procedure. Thus, the selection of study candidates for Barrett's eradication should involve a consideration of the esophageal cancer risk.

For patients who have Barrett's esophagus without dysplasia, modern studies suggest that the risk of cancer development is approximately 0.5% per year [11]. An evidence-based tool that can be used to help decide whether the potential benefits of a treatment outweigh its disadvantages is the calculation of the number needed to treat (NNT) [20]. This is done using the formula NNT = 1/ARR, where ARR is the absolute risk reduction achieved by the treatment. Assume, for the sake of argument, that an endoscopic eradication procedure is perfectly effective and completely eliminates the risk of cancer development. This represents an absolute risk reduction of 0.5%. Therefore, the NNT = 1/0.5 = 200. If this highly optimistic assessment of risk reduction attributable to ablation of Barrett's epithelium is correct, then there would be a need to treat 200 patients in order to prevent one cancer in 1 year. Such a large NNT might be acceptable for a treatment that is safe, inexpensive, and convenient, but no endoscopic ablation technique meets all of those criteria. Regarding the safety issue for this example, the mortality rate for an eradication would have to be considerably lower than 1 in 200 to justify the procedure. Otherwise, more patients would succumb to the procedure than to the cancer it tries to prevent.

One could argue that the above estimate of NNT is unfair because it considers the number of procedures needed to prevent cancer for only 1 year, whereas a successful endoscopic ablation might prevent cancer for a lifetime. This may be true. However, Barrett's metaplasia often persists or recurs after endoscopic ablation. Thus, even an apparently successful ablation procedure may not confer lifelong protection from malignancy. Furthermore, the NNT calculation used in this example is based on a reduction of absolute risk that has not been established. It is not clear that ablation of nondysplastic Barrett's epithelium reduces the risk of cancer development at all, let alone completely.

In addition to reducing the risk of esophageal cancer development, another potential benefit of ablating nondysplastic Barrett's esophagus would be the elimination of the need for lifelong endoscopic surveillance, with all of its attendant expense, inconvenience, and risk. As mentioned, however, the long-term benefit of ablation in reducing cancer risk has not been established, and the potential for cancer developing from buried metaplasia or from regrowth of Barrett's epithelium after ablation remains an unresolved issue. Without definitive data on cancer risk reduction, it is not appropriate to terminate endoscopic surveillance after eradication on the basis of the dubious assumption that the cancer risk has been eliminated. We conclude that available data do not support the routine application of endoscopic ablative therapy for patients who have Barrett's esophagus without dysplasia, outside of trials. Nevertheless, the concept that a one-time ablation procedure might obviate lifelong endoscopic surveillance is appealing, and further studies in this area are warranted.

Barrett's esophagus with dysplasia

Cancers in Barrett's esophagus evolve through a series of genetic alterations that endow cells with growth advantages. With the accrual of sufficient, growth-promoting mutations, the cells become autonomous and lose their responsiveness to stimuli that ordinarily would retard growth. This autonomous condition is called neoplasia. Before neoplastic cells become malignant, the mutations that confer growth advantages also may cause histological changes in the tissue that pathologists can recognize as dysplasia (also called intraepithelial neoplasia). For patients with dysplasia in Barrett's esophagus, the risk of progression to invasive cancer is substantially higher than that of patients without dysplasia. For an effective eradication procedure, a higher cancer risk translates into a lower NNT and a higher tolerance for procedure risk.

Data on the risk of cancer progression for patients with dysplasia in Barrett's esophagus are limited and flawed [21]. As noted above, a major problem that confounds the interpretation of these studies is that of interobserver disagreement among pathologists in the scoring of dysplastic changes. Histological changes similar to those of low grade dysplasia (LGD) can be seen in non-neoplastic tissue that is regenerating in response to injury, making it difficult for pathologists to distinguish LGD in Barrett's esophagus from reactive changes caused by reflux esophagitis. Interobserver agreement among experienced pathologists for the diagnosis of LGD can be less than 50% [21]. Interobserver agreement is better (approximately 85%) for high grade dysplasia (HGD), but far from perfect. There is also substantial disagreement among pathologists when distinguishing HGD from intramucosal carcinoma, a lesion which has potential for lymphatic dissemination [22]. The problem of interobserver disagreement among pathologists is especially severe for LGD, rendering data on the natural history of this condition especially unreliable. For example, one group of investigators followed 25 patients with LGD for a...
mean duration of 26 months, during which five (20%) progressed to HGD and two (8%) progressed to adenocarcinoma [23]. However, progression to a higher grade was seen in seven of the 17 patients (41%) for whom at least two of the three study pathologists agreed on the diagnosis of LGD, whereas progression was seen in four of the five patients (80%) for whom there was unanimous agreement among the study pathologists. A more recent study that included 156 patients with LGD found that the incidence of cancer in those patients was 0.6% per year, a rate not substantially higher than that for patients without dysplasia [14]. Even if the rate of progression to cancer in LGD is as high as 1% per year, the associated NNT of 100 for a perfect eradication procedure to prevent one cancer in 1 year remains a daunting figure. Therefore, we do not yet recommend eradication procedures for patients with LGD in Barrett’s esophagus, outside of clinical study protocols. As suggested above, more rigorous evaluation of histological LGD specimens might allow isolation of a subgroup of LGD patients with sufficiently high cancer risk to be appropriate for intervention outside of clinical trials; however, this remains to be demonstrated.

Patients with HGD in Barrett’s esophagus progress to adenocarcinoma at the rate of approximately 4% to 6% per year [14, 21]. If one assumes a rate of cancer progression of 5% per year, then the NNT for a perfect eradication procedure to prevent one cancer in 1 year is only 20. Such an NNT could justify a relatively expensive and somewhat risky eradication procedure, especially considering the alternative therapeutic options of esophagectomy or intensive surveillance with endoscopy performed every 3 months indefinitely.

Characteristics other than dysplasia

Beyond dysplasia, other patient characteristics likely color the outcome of ablation trials. For instance, some trials have concentrated on elderly patients with dysplasia who were not good surgical candidates [24]. This approach has the benefit of not denying, in favor of investigatory approaches, potentially curative therapy with a proven record to appropriate patients. However, the mortality from causes other than esophageal carcinoma can be so high that it obscures any potential benefit from the therapy itself. In such settings, even delaying progression to cancer for only a short period of time might appear to be definitive therapy due to death from competing causes. Other patient factors, such as the presence of a surgical antireflux procedure, might also impact patient outcomes. If fundoplication leads to regression of Barrett’s esophagus without further intervention, as has been suggested by some literature [25], the presence of such patients in ablation trials would artificially improve outcomes.

What are the appropriate clinical outcome variables for ablation trials?

Efficacy variables

The purpose of eradicating Barrett’s epithelium is to prevent the development of esophageal adenocarcinoma. Ideally, therefore, a study on the efficacy of an eradication technique would use the cancer development rate as its primary outcome variable. When designing such a study, however, it is important to consider the issue of what constitutes adequate follow-up. Specifically, how long must one wait to conclude that the cancer risk has been eliminated by the treatment? Patients treated for epithelial carcinomas traditionally have been deemed cured if there is no evidence of recurrence at 5 years, because it is assumed that any cancer stem cells that survived the treatment would have become clinically manifest within that time period. As discussed above, however, it often takes considerably longer than 5 years for dysplasia to progress to invasive cancer, and nondysplastic Barrett’s metaplasia usually does not progress to cancer during a patient’s entire lifetime. Therefore, a study using the cancer development rate as its primary outcome variable will require large patient numbers and long durations of follow-up. The expense and duration of such a study may render its conduct impractical. In this case, an investigator may choose to use a more readily obtainable surrogate marker for decreased cancer risk as an outcome variable.

Surrogate markers that might be used to indicate that an eradication procedure has decreased the cancer risk include the complete eradication of dysplasia or the complete eradication of all Barrett’s epithelium (both dysplastic and nondysplastic). These end points can be assessed soon after application of the eradication procedure. Although a number of eradication studies have reported rates for partial regression of neoplasia (e.g., cancer to HGD, HGD to LGD) or partial regression of nondysplastic Barrett’s epithelium [24, 25], these are less desirable end points because it is not clear how such partial regression affects the cancer risk. The complete eradication of dysplasia suggests that the cancer risk may be decreased, but if metaplasia persists then there is the possibility of the future development of neoplasia and the possibility that dysplastic epithelium is still present but has been missed because of biopsy sampling error. The most rigorous surrogate end point is the complete eradication of all Barrett’s epithelium.

Even the apparently complete eradication of all Barrett’s epithelium does not guarantee that the cancer risk has been eliminated, one reason why the cancer risk might persist is the possibility that the eradication procedure caused squamous epithelium to grow over foci of Barrett’s epithelium (so-called “buried” metaplasia, Fig. 2). These foci are not apparent endoscopically and generally can be detected only by obtaining random biopsy specimens of the previously ablated esophageal area that has been covered by neosquamous epithelium. However, buried metaplasia can be easily missed as the result of biopsy sampling error. Superficial biopsy specimens of squamous epithelium that do not provide at least some lamina propria are not informative for buried metaplasia, and endoscopic biopsy specimens of squamous epithelium often are superficial. It is conceivable that the tissue remodeling that takes place after some eradication procedures might render the neosquamous epithelium even more difficult to penetrate with biopsy forceps, resulting in biopsy specimens that are even more superficial. Short of resecting the esophagus and examining its full thickness histologically, it is virtually impossible to exclude the possibility that there are foci of buried metaplasia.

Another reason why even complete eradication of Barrett’s epithelium may not eliminate the cancer risk is that ongoing GERD may result in the reappearance of Barrett’s metaplasia. For patients with dysplasia, furthermore, it is conceivable that the genetic abnormalities acquired during the development of neoplasia might convey survival advantages that make the neoplastic cells resistant to eradication therapies. In this situation, those therapies might be better suited for destroying normal cells than neoplastic ones. Therefore, a therapy that does not destroy all of the neoplastic stem cells conceivably might even hasten carcinogenesis by causing further genetic damage
to the neoplastic cells, by stimulating their further proliferation and by removing non-neoplastic cells that otherwise might help to constrain the neoplasm. Presently, this is a theoretical concern only. We know of no study suggesting that ablation therapy facilitates carcinogenesis in Barrett’s esophagus. Although the complete eradication of all Barrett’s epithelium, dysplastic and nondysplastic, may be the most rigorous available surrogate marker for decreased cancer risk, for the reasons discussed above, assurance that the cancer risk has indeed been reduced will require long-term follow-up studies. Consequently, it will be some time before patients can be assured of the efficacy of the new eradication procedures.

Safety variables
Given the benign course of most cases of Barrett’s esophagus, quantifying adverse outcomes in ablation trials will be key to performing informed risk-benefit analysis of the procedures. For most potential complications of ablation, no “industry standard” has emerged to either define the complication or quantify its severity. For instance, in some trials, a diagnosis of esophageal stricture requires both the endoscopic appearance of narrowing as well as the report of dysphagia, while in other studies, an endoscopic appearance of narrowing alone is adequate to make this diagnosis. Resolution can be similarly vague. Has stricture resolution occurred when endoscopic dilation results in resolution of dysphagia? Or must the esophagus display a normal caliber? What is the likelihood that a previously strictured esophagus will ever appear totally normal again? The answers to questions such as these will determine how damaging the intervention appears.

Similarly, it is also difficult to quantify other potential adverse outcomes, such as chest pain or bleeding. While some studies have quantified chest pain using Likert scores or visual analogue scales, such approaches are of unclear validity, and likely suffer from ceiling effects. The degree of bleeding that defines a clinically significant adverse event has been variable. Is scant hematemesis sufficient? Or is hospital admission or even blood transfusion necessary?

In an effort to standardize the approach to complications, we suggest that investigators use an accepted system for coding adverse events, such as the Medical Dictionary for Regulatory Activities (MedDRA). Such systems standardize adverse outcomes, to avoid multiple variants of the same event (ex, GI bleeding vs. gastrointestinal hemorrhage), and provide explicit criteria for classification of the severity of the event.

Conclusion
The ablation trials are a heterogeneous collection of data, demonstrating marked diversity in the patients enrolled, protocols for assessment of effect, and primary and secondary outcomes used. The heterogeneity of these trials and lack of standardization of several cardinal variables common to all the trials im-

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Table 1  Critical elements of trials of ablation in Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Study element</th>
<th>Suggested approach</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>Disease definition</td>
<td>Patients with both the endoscopic appearance of Barrett’s esophagus and specialized intestinal metaplasia on biopsy</td>
<td>Comparability to previous studies; uncertainty of natural history and cancer risk in non-goblet CLE</td>
</tr>
<tr>
<td>Study design</td>
<td>As possible, a concurrent or historical control group; RCT optimal</td>
<td>High rates of sampling error and possible spontaneous regression of Barrett’s esophagus inflate therapeutic benefit; allows comparison of quality of life and side-effects of therapy</td>
</tr>
<tr>
<td>Patient population</td>
<td>Dysplastic and nondysplastic patients may both be ethically considered for trials</td>
<td>Enrolment of dysplastic patients is attractive because of the ability to use cancer outcomes; enrolment of nondysplastic patients in trials is ethical, and often performed as proof of principle, but the utility of data is limited by the use of surrogate outcome markers because of the low rates of progression to cancer</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Objective, easily quantifiable measures, such as cancer incidence, cancer death, complete eradication of intestinal metaplasia, or complete eradication of dysplasia are preferred</td>
<td>Subjective assessments, such as percentage of columnar tissue eradicated are subject to observer bias; clinical relevance of transient disappearance of dysplasia or intestinal metaplasia, during a trial is of unclear clinical significance</td>
</tr>
<tr>
<td>Classification of adverse events</td>
<td>Use of a codified system of adverse outcomes</td>
<td>Avoids the variable classification of adverse events found currently in trials, and allows comparisons across studies; lessens potential bias by providing concrete measures for severity of outcomes</td>
</tr>
<tr>
<td>Presentation of data</td>
<td>Primary analysis should be intention-to-treat</td>
<td>Lack of compulsory accounting for all patients in study may obscure the toxicity or practical difficulties of applying the intervention; Per protocol analyses may inflate the reported benefits of the intervention</td>
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RCT, randomized controlled trial; CLE, columnar-lined esophagus.
pedes our understanding of these methods and essentially renders it impossible to make meaningful comparisons across ablation techniques. Table 1 summarizes critical study elements in trials of ablation in Barrett's esophagus, and possible interventions designed to improve our methodology in these studies. Further work defining “industry standards” for simple questions, such as: “What is Barrett's esophagus?,” “Who has Barrett's esophagus?,” “What defines 'success' in a Barrett's esophagus trial?,” and “How are we going to endoscopically assess the post-ablation Barrett's esophagus patient?,” will be necessary to optimize our understanding of the value of these interventions.

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