Editorial Commentary

Time to define long-term outcomes after Barrett's endoscopic therapy

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Barrett's esophagus (BE) is a known precursor to esophageal adenocarcinoma (EAC). While the incidence of EAC is rising, especially in the young, most are still detected at an advanced stage with a poor 5-year survival (1,2). Current efforts are aimed at early detection and therapy of superficial EAC (and high-grade dysplasia; HGD) while screening strategy is still evolving. We do know that Barrett's endoscopic therapy (BET) aimed at Barrett's dysplasia and EAC is effective aiming to resect visible neoplasia and remove all remaining Barrett's epithelium (3,4). Therefore, BET is current standard of cure for dysplasia and cancer limited to mucosa (T1a) (5,6). Endoscopic resection is the standard tool for diagnosing, staging and possible curative resection of raised or visible lesions, while radiofrequency ablation (RFA) is the standard ablation modality with strong data on efficacy at complete eradication of remaining neoplasia (CE-N) and intestinal metaplasia (CE-IM). Therefore, current guidelines support BET for HGD/EAC with goal for removal of all remaining Barrett's epithelium (5-7).

However, durable efficacy (at least 5 years of sustained CE-IM) is not available from high-quality, robust, prospective data from randomized controlled trials (4). Most data on substantial benefit of BET for CE-N/CE-IM is driven from retrospective registries from centers of expertise. When existing studies were examined through a stringent-selection criteria of definitions of BE eradication, methodology and follow up post BET, either studies lack a standard BET protocol, do not provide information over 5 years and/or suffer from significant attrition bias (4). Despite high efficacy of BET reported across studies immediately after therapy completion (pooled CE-N: 95.9%; CE-IM: 90.9%), this declined by ~10% after only 3.4 years of follow-up to CE-N of 89% and CE-IM of 77.8%. In addition, only two studies reported a post-BET follow-up of >5 years with sustained CE-IM in only 50% subjects (4). A higher person-years of follow-up was seen to correlate with a decrease in BET efficacy in this analysis. There was a high rate of IM recurrence which could be managed endoscopically, however, concern remains if this increases further as years out of BET increases and there is lack of standard practice currently. In addition, apart from initial CE-N resolution, we do not know whether there is recurrence of CE-N (after initial CE-IM of 1 year) as data is not available from large, prospective studies of these subjects over long term for variety of reasons including advanced age, death, loss to follow up and study termination.

Recently, van Munster and colleagues reported short-term and long-term outcomes for 1,386 patients treated over 10 years with uniform treatment and follow-up (8). BET protocol is centralized in nine expert centers in The Netherlands with endoscopists and pathologists following a specific protocol and data was prospectively collected via a uniform database. Patients with low-grade dysplasia/HGD or low-risk cancer, were treated by endoscopic resection of visible lesions followed by trimonthly RFA sessions of any residual BE until CE-IM was achieved. Durability was defined as having follow up of at least 1 year after CE-IM. Authors did not include those patients who had only endoscopic resection. After initial CE-IM in 94%

(1,270/1,348), 1,154 were assessed for long-term outcomes. During median 43 months (22 to 69) and 4 endoscopies (1 to 5), 38 had recurrence of dysplasia (3%, annual recurrence risk 1%), all were detected as endoscopically visible abnormalities. Random biopsies from a normal appearing cardia showed IM in 14% and neoplasia in 0%, however, only one third had cardia-IM on follow-up and none progressed to cancer. Authors provide data from expert centers over 10 years with centralized care showing that RFA+/– endoscopic resection is effective with low recurrence rate for dysplasia. This data also favors stretching out follow up intervals and questionable utility of biopsies from cardia and neo-squamous epithelium. Importantly, recurrence rate was 1% per year and most are detected endoscopically. This underscores the important aspect of a high-quality endoscopy exam each time. Histology was low-grade dysplasia in one-third cases and touch up therapy was done in ~40%. Median duration of follow-up after therapy completion was approximately 2.5 years. Most common cause of death was non-EAC neoplasms followed by cardiovascular disease. Information regarding adherence to acid-suppression is not provided. Contrary to a recent study of 10-year outcomes from UK RFA registry reporting a 4.1% cancer-rate from Kaplan-Meir estimate after 10 years of therapy and Barrett's recurrence in up to 18% after CE-IM at 8 years (9), longer-term outcomes are currently not available from this cohort.

Overall, this nation-wise cohort study of expert centers provides a useful homogenous protocolized practice data of BET efficacy lasting over 3 years in majority (up to 7 years in a proportion) (8). In addition, it does provide strong data regarding low utility of cardia biopsy, natural history of cardia IM post BET and need for a high-quality exam. Question of defining and standardization of BET protocol and post BET definitions still prevail which will need to be explored in a consensus or expert panel meeting followed by validation. Data from nationalized cohorts are useful but difficult to generalize due to variation in practices across the globe, however, it does provide a framework that can be adopted and modified. There is a need for high-quality studies of post BET outcomes reporting and demonstrating sustained durability, detection and management of post BET recurrence, salvage options and determining surveillance patterns post BET. As authors have shown in this study, after its immediate effect, BET efficacy can be sustained if strict adherence to treat to target and close surveillance is followed. Future efforts should focus on standardizing the methodology and outcome reporting which would help eliminate significant heterogeneity in existing evidence. Definition of BET protocol is necessary to guide future clinical trials of new modalities as well. This will establish consistency among future studies and allow comparison across studies of same and various modalities. Efforts aimed at establishing these definitions should be the next step in BE research.

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Footnote

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