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RISKS FACTORS WITHIN BARRETT'S OESOPHAGUS: A REVIEW

Internal Medicine

Dr. Gayathri Jayakumar Resident Doctor.

Dr. Mohammad Sanim Yasar* IMT – 1. *Corresponding Author

ABSTRACT

There are many alternatives for treating Barrett's oesophagus (BE) with high-grade dysplasia (HGD) in the age of minimally invasive therapy. However, without precise criteria, the standard of treatment is still up for debate for many patients because therapy is customised. This review's objectives are to briefly introduce and contrast current therapeutic modalities, with a focus on endoscopic approaches, list factors that can help choose the best course of action (medical, endoscopic, or surgical), and highlight the dearth of well-designed studies that compare the results of these therapies to date. BE, the final stage of the disease's natural progression, is caused by chronic gastro-oesophageal reflux disease (GERD). In the United States, 20% of people are thought to have gastro-oesophageal reflux disease, and 10% of those patients are diagnosed with BE. BE is frequently seen during an endoscopy to assess GERD symptoms. While the chronicity of GERD symptoms may be associated with the potential for BE transition, the severity of GERD symptoms is not thought to be a sign of BE existence.

KEYWORDS

Barrett's Oesophagus, high-grade dysplasia, low grade dysplasia, gastro-oesophageal reflux disease

INTRODUCTION

There are many alternatives for treating Barrett's oesophagus (BE) with high-grade dysplasia (HGD) in the age of minimally invasive therapy. However, without precise criteria, the standard of treatment is still up for debate for many patients because therapy is customised. This review's objectives are to briefly introduce and contrast current therapeutic modalities, with a focus on endoscopic approaches, list factors that can help choose the best course of action (medical, endoscopic, or surgical), and highlight the dearth of well-designed studies that compare the results of these therapies to date.

BE, the final stage of the disease's natural progression, is caused by chronic gastro-oesophageal reflux disease (GERD). In the United States, 20% of people are thought to have gastro-oesophageal reflux disease [1], and 10% of those patients are diagnosed with BE.[2] BE is frequently seen during an endoscopy to assess GERD symptoms. While the chronicity of GERD symptoms may be associated with the potential for BE transition, the severity of GERD symptoms is not thought to be a sign of BE existence.[3]

Long-term exposure of the oesophageal mucosa to stomach acidity has been shown to cause cellular damage to the stratified squamous epithelium and to provide an aberrant environment that promotes intestinal epithelial metaplasia, a type of repair.[4,5] Additionally, BE is linked to a functional abnormality of the oesophageal body, a severe mechanical insufficiency of the lower oesophageal sphincter, and inadequate oesophageal clearance.[6–8] In BE, a pathological, specialised columnar epithelium that is neither of the stomach nor the heart type but rather has characteristics of the intestinal type of epithelium replaces the stratified squamous epithelium that normally lines the oesophageal mucosa.[4] DNA changes that lead to cancer are typically seen in this diseased kind of epithelium.[2,9,10]

Depending on whether or not they show dysplasia, the changes in BE are histologically divided into three groups: (1) BE without dysplasia; (2) BE with low-grade dysplasia; and (3) BE with HGD.[11–13] Dysplasia in BE with HGD is limited to the mucosa and does not extend past the basement membrane. In contrast to invasive adenocarcinoma, which occurs when dysplasia penetrates the muscularis mucosa layer, intramucosal (superficial) adenocarcinoma occurs when it spreads past the basement membrane and into the lamina propria through the a propria through the in-coming lymphatic network. Therefore, BE with HGD is thought to be a precursor of E with HGD, which is thought to be a forerunner of invasive adenocarcinoma.

Risk Groups For The Neoplastic Progression Of Barrett's Oesophagus

Risk variables for progression are a crucial component of Barrett's oesophageal surveillance decisions because of the wide range of progression rates among patients with the condition. Only two risk factors—the Barrett's oesophageal segment length and the histopathologic grading of dysplasia—are used to determine the current Barrett's oesophageal monitoring intervals. Indefinite dysplasia (IND) and low-grade dysplasia (LGD) should be closely monitored, according to the standards, and treated if LGD is verified twice.[14,15]

Demographic Factors

White Caucasians are more likely to have Barrett's oesophagus and EAC, but nothing is known about whether ethnicity influences advancement.[16] At a level comparable to that documented for Barrett's oesophageal development, male gender [OR, 2.12; confidence interval (CI), 1.78-2.52] and age (OR, 1.03 per unit increase; CI, 1.01-1.05) are linked to an elevated risk for progression.[17] However, we should be aware that these risk estimations might be erroneous due to the low proportion of women in Barrett's oesophageal cohorts. Women's annual progression rate to HGD/EAC was much lower than men's (0.05% vs. 0.3%, N = 324 vs. 1,821) in a pooled research from six centres; yet, the percentages of patients who progressed towards LGD were intriguingly similar (12.0% vs. 15.2%;).[18]

Only one study examined the relationship between a positive family history and the advancement of BE, despite the fact that it is a substantial risk factor for a diagnosis. A potential correlation between early illness onset and the number of afflicted family members was proposed in a sizable cohort of individuals with Barrett's oesophagus, or EAC. Although this link lost significance in a multivariate logistic regression, patients with more than three afflicted individuals received their HGD or EAC diagnosis at a younger age of 56 years as opposed to those with less than two affected members who received their diagnosis at a median age of 64 years.[19] Even after adjusting for other variables such age, sex, and Barrett's oesophageal length, smoking remains a weak-moderate risk factor (OR, 1.53; CI, 0.94-2.48) for the development of HGD/EAC.[17] Although obesity has been associated to the formation of Barrett's oesophagus, there is currently no evidence linking obesity to the advancement of neoplasms, and alcohol does not appear to play a part in this process.[17]

Endoscopic Factors

Although longer segments are known to be associated with a higher risk of neoplastic development, the guidelines' cutoffs appear to be a little arbitrary. The European Society of Gastrointestinal Endoscopy recommends annual endoscopy for segments longer than 10 cm and three-year surveillance for segments longer than 3 cm. They further recommend that these procedures be carried out in Barrett's oesophagus expert centres. The American College of Gastroenterology recommends 3-5 years of monitoring, with no

specified length, while the British Society of Gastroenterology recommends 2-3 years of surveillance for segments longer than 3 cm.[14,20,21] An OR of 1.25 (CI, 1.16-1.36) per centimetre for progression to HGD/EAC in NDBE/LGD patients was reported in one systematic review [17]. Another systematic review that only included NDBE patients revealed 0.24% annual progression rates for short segment Barrett's oesophagus (<3 cm) versus 0.53% for long segments (>3 cm; ref.).[20] Another study Anderson LA et al observed that, Barrett's disease was linked to gastro-oesophageal reflux [OR 12.0 (95% CI 7.64-18.7)]. Adenocarcinoma of the oesophagus [OR 3.48 (95% CI 2.25-5.41)]. Compared to controls, individuals with oesophageal adenocarcinoma were more likely to have a high body mass index [OR 2.69 (95% CI 1.62-4.46)] and to have smoked in the past or currently [OR 1.72 (95% CI 1.06-2.81) and OR 4.84 (95% CI 2.72-8.61) respectively]. There were no discernible correlations found between Barrett's oesophagus and these risk variables. Oesophageal adenocarcinoma was negatively correlated with fruit but not vegetables [OR 0.50 (95% CI 0.30-0.86)].[22] While there is some direct evidence that a longer BE segment is associated with a higher risk, bigger cohort studies are needed to determine optimum cutoffs and rule out dubious Barrett's diagnoses for segments shorter than 1 cm.

Histopathologic Factors

According to the Vienna classification, IND is diagnosed when a pathologist finds atypical cells and aberrant architecture that are insufficient to diagnose dysplasia. Even while patients with IND have a modest progression rate to HGD/EAC, the risks are still almost three times higher than those with NDBE, demonstrating that this is a significant risk factor. Because of the uncertainty surrounding the diagnosis, the risk varies. While a significant number of patients just have active inflammation, in rare cases, this can indicate true dysplasia.[23,24] Therefore, after an IND diagnosis, sufficient acid suppression is the first step to assist resolve the diagnostic confusion brought on by inflammation, and prolonged IND is a substantial risk factor (OR, 3.2; CI, 1.04-9.98).[25] Aberrant expression of the p53 protein is another biomarker that can be used to differentiate between inflammatory atypia and genuine dysplasia. A more conclusive diagnosis could result from p53 IHC, which could also improve intraobserver agreement amongst pathologists.[26] With annual rates in the literature ranging from 4.2 to 6.7 per 100 person-years moving to HGD/EAC, LGD is a significant risk factor for Barrett's oesophageal development.[17,27,28], but as was already indicated, pathology assessment is infamously challenging and prone to intraobserver disagreement.[29,30] A second pathologist's confirmation is crucial since the annual neoplasia advancement rate rises with each additional pathologist who confirms the degree of dysplasia. For HGD/EAC, this rate can rise to 20% when three qualified pathologists confirm it.[29] Furthermore, as normal clinical laboratories become more familiar with this highly specific biomarker, p53 IHC may be able to replace the need for a second confirmation procedure by improving intraobserver agreement.[31]

Risk Stratification in Clinical Practice; Triaging Upfront

A number of clinical risk stratification tools have been created based on these established risk indicators to help with patient decision-making. Parasa and colleagues' study, which included 2,697 patients and examined 11 parameters, describes the clinical risk classification model that was tested in the largest dataset. The final model incorporated four risk factors: baseline LGD, smoking, Barrett's oesophagus length, and gender.[32] Proton-pump inhibitors (PPIs), NSAIDs, aspirin use, age, race, and hiatus hernia were taken into account, but no correlation was discovered. To anticipate the annual progression risk, three categories were developed: low (annual risk 0.13%), moderate (0.73%), and high (2.10%). It was recommended that the lower risk group stop observation.

Two more investigations [33,34] validated this model and showed a similar AUC of 0.70; however, in Nguyen and colleagues' analysis, this was accomplished by reclassifying the model into high- and low-risk categories using a different cutoff. Overall, there is a 21% stratification benefit when male sex and smoking are included in the model as opposed to the clinically used risk factors of Barrett's oesophageal length and dysplasia.[33]

A straightforward test might be added to the triage process prior to endoscopy as an auxiliary to clinical risk factors. Cells are extracted from the oesophagus's length using the nonendoscopic capsule-on-a-string Cytosponge-TFF3 test (Medtronic UK) so that a panel of biomarkers may be evaluated in a lab. The procedure is less intrusive, more expensive, and well-tolerated than a standard oesophagoduodenoscopy (OGD).[35] The panel was simplified to make clinical implementation easier, and a retrospective cohort of 891 patients split into training and validation sets showed that p53 IHC in conjunction with any cytologic atypia is very effective at prioritising patients for endoscopy, with an AUC for HGD/EAC of 0.86 in the validation cohort.

The AUC for HGD/EAC rose to 0.91 when clinical risk indicators (sex, age, and Barrett's oesophageal segment length) were included to define a moderate-risk group that requires more frequent surveillance.[35] A direct comparison with endoscopic biopsies obtained during the same endoscopy served as the gold standard for all of these investigations. This increases the Cytosponge test's potential for utility in risk classification for Barrett's oesophageal patients, and additional prospective analysis of this method is currently being conducted (ISRCTN91655550).

Risk Assessment In Clinical Practice: Innovative Biomarker Instruments Utilised For Endoscopy Samples

Along with molecular indicators that can enhance risk classification, new wide-field sample tools have surfaced to complement conventional biopsy during endoscopy. However, it has long been known that abnormal protein expression of the tumour suppressor gene TP53 increases the likelihood of malignant development.[28,36] A major risk factor for neoplastic development with a risk comparable to LGD was abnormal p53 expression (overexpression or deletion), according to a systematic analysis that examined 12 studies (OR, 7.04; 95% CI, 3.68-13.46). With ORs for LGD of 8.64 (95% CI, 3.62-20.62) and NDBE of 6.12 (95% CI, 2.99-12.52), this risk exists regardless of dysplasia status.[36] Using a more sophisticated score for the IHC staining, progression could also be predicted in certain cases before phenotypic signs of dysplasia. The usefulness of a p53 IHC was recently confirmed in a large prospective trial comprising 1,438 patients with NDBE and LGD.[37]

Using standard paraffin-embedded biopsies, TissueCypher (Castle Biosciences, Inc.) is a pathologic assessment tool that combines fluorescence imaging of biomarkers with morphologic variables, containing 15 characteristics. A machine learning algorithm that divides patients into three risk categories (high, intermediate, and low) is used in the analysis, which is carried out in a centralised, commercial laboratory. For the high-risk category, a recent pooled analysis of four case-control studies—NDBE, IND, and LGD—showed a 98% specificity for predicting neoplasm, but a poor sensitivity of only 38%. Combining the high- and intermediate-risk groups could boost the sensitivity to 55% at the expense of specificity.[38] It should be mentioned that the same research team demonstrated that because of the assay's high cost and complexity, cost-effectiveness can only be achieved at a sensitivity of at least 50%.[39] The benefits of the TissueCypher assay test for LGD appear to be more obvious; it has the potential to reclassify 50% to 56% of patients as progressors after the pathologist first downstaged them to NDBE.[40]

An endoscopic brush that offers deeper sampling of the Barrett's mucosa over a larger surface area is called the Wats3D, or Wide Area Transepithelial Sampling with Three-Dimensional Computer-Assisted analysis (CDx Diagnostics). Following sample submission to a central laboratory, a pathologist confirms the presence of dysplastic cells in a computer-aided study of the cytologic specimen. Wats3D resulted in an additional 213 dysplasia diagnosis in a large multicenter trial that included both screening and surveillance cases; 10 of these cases were "missed" with biopsies for HGD/EAC. The authors concede that it is impossible to establish the benefit when compared to expert endoscopies because adherence to the Seattle procedure was not monitored.[41]

CONCLUSION

These findings indicate that patients with Barrett's oesophagus have a significant lifetime chance of developing high-grade dysplasia or cancer. With the exception of those performed for therapeutic interventions to the metaplastic section, follow-up for high-grade dysplasia, malignancy, or endoluminal treatment, the overall burden of surveillance endoscopies is 9.8 per patient.

We accept that there are information gaps regarding all of these developments and that additional validation is required for the data for

the new devices and tests. Health economic studies are also necessary to balance the risks and advantages of the monitoring processes and to identify the best trade-offs in terms of health care expenses for the health care system. But without slowing down, we can begin collecting this data on the scale needed to get the answers with careful implementation study.

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