Biomarkers in Barrett's Esophagus

Role in Diagnosis, Risk Stratification, and Prediction of Response to Therapy

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KEYWORDS

• Biomarkers • Diagnosis • Screening • Risk stratification • Barrett's esophagus
• High-grade dysplasia • Esophageal adenocarcinoma • Response to therapy

KEY POINTS

- Molecular diagnosis of Barrett's esophagus (BE) can now be performed on nonendoscopic cytology specimens. Trefoil factor 3 is promising. Other markers to test further are microRNA and methylated genes.
- BE can be risk-stratified by measuring global (eg, aneuploidy, multiple gains) or specific (eg, p53 expression) markers. A biomarker panel is likely to be needed.
- Limited data are available on markers that can predict response to therapy. Chromosome and gene loss/gain by fluorescent in situ hybridization may be of value.
- P53 mutational analysis on nonendoscopic cytology specimens can detect prevalent high-grade dysplasia. Thus, the same sample can be used to screen for and risk-stratify BE.

INTRODUCTION

Extensive biomarker research has been conducted to improve the diagnosis and management of Barrett's esophagus (BE). Investigators have worked for many years to discover biomarkers for BE diagnosis, risk stratification, and prediction of response to therapy. The level of evidence required to change clinical practice has generally not been achieved, with the exception of p53; however, more investment and

Conflicts of Interest: Dr A. Bansal has filed a provisional patent application related to microRNA for BE diagnosis and risk stratification. Dr R.C. Fitzgerald is named on patents pertaining to the Cytosponge that has been licensed by the Medical Research Council, UK to Covidien GI Solutions.

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collaborative studies are starting to pay dividends.[1] Discovery of clinically applicable biomarkers for BE management has never been more important. The risk of progression of BE to cancer is lower than previously thought.[1–3] Therefore, the resources need to be focused on those BE patients who are most likely to benefit. An important hurdle to clinical application of biomarkers is that specimen acquisition to study biomarkers requires an endoscopy; this has changed recently with the availability of a well-tolerated, easy-to-swallow capsule-based cytology sponge that can collect esophageal cells in an office-based setting.[4] Also, emerging data suggest that blood samples can be used to study the disease status.[5,6] Last, genome-wide next-generation sequencing techniques[7] have significantly added to the understanding of somatic DNA aberrations in BE pathogenesis. All of these factors have created a viable environment for molecular biomarkers of BE and associated risk of cancer to progress to the clinic. In the following sections, important biomarkers to diagnose BE, risk-stratify the patients with BE, and identify those BE patients who are likely to be less responsive to endoscopic therapies are discussed. Where possible, studies published in the last 5 years were the focus.

BIOMARKERS FOR BARRETT'S ESOPHAGUS DIAGNOSIS

Most biomarker research has focused on risk stratification in BE discussed elsewhere in this review. Lately, there has been renewed interest in molecular testing for BE diagnosis. Recent technological developments in esophageal sampling in combination with specific markers have made office-based diagnosis of BE possible. Therefore, widespread application of these tests for BE diagnosis in persons at clinically significant risk for BE may become a viable option. These markers are described in later discussion.

Trefoil Factor 3

Introduction

Trefoil factor 3 (TFF3) is a secretory protein expressed in the goblet cells of the intestinal mucosa that has shown significant promise for molecular BE diagnosis.[4,8]

Studies

To discover BE-specific markers, Lao-Sirieix and colleagues[8] analyzed publicly available microarray datasets that compared normal squamous, BE, and gastric mucosa. Validation by 2 techniques, polymerase chain reaction (PCR) and histochemistry, suggested that TFF3 may be a specific marker for BE-type epithelium. TFF3 as a biomarker for BE diagnosis was tested on specimens acquired via a novel proprietary nonendoscopic cytology sponge within a capsule. After an initial study showed feasibility,[8] the same group of investigators conducted a study in the primary care setting and found the capsule-based cytology sponge to be well tolerated with successful ingestion in 99% of 504 subjects.[4] The sensitivity and specificity of TFF3 expression on cytology samples for diagnosis of circumferential BE 1 cm or longer were 73.3% (95% confidence interval [CI] 44.9%–92.2%) and 93.8% (91.3%–95.8%), respectively. These numbers improved to 90.0% sensitivity (95% CI 55.5%–99.7%) and 93.5% specificity (95% CI 90.9%–95.5%) when BE segments 2 cm or longer were included in the analysis. This approach was recently examined in a larger trial (**Box 1**).

Summary

These results make a strong case for molecular testing on a nonendoscopic cytologic specimen as a practical tool for BE diagnosis in the symptomatic population, most of whom are not investigated. Further studies are ongoing to evaluate the applicability of this strategy to other populations.