Molecular Detection of Gastrointestinal Neoplasia

Innovations in Early Detection and Screening

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KEYWORDS

• Gastrointestinal cancer • Early detection • Screening • Molecular markers
• Blood testing • Stool testing

KEY POINTS

- Gastrointestinal (GI) malignancies account for 40% of all cancer deaths globally, but most types remain unscreened.
- With recent technology advances, new molecular screening tools under development could open doors for early detection of all GI cancers.
- Adjunctive molecular tests also have potential to extend the reach of the endoscopist for greater accuracy in detecting GI neoplasms.

INTRODUCTION

Globally, gastrointestinal (GI) malignancies account for roughly 40% of all cancer deaths.[1,2] In the United States, upper GI cancers kill twice as many as does colorectal cancer (CRC); but, unlike CRC, rates for cancers of the pancreas, liver, and esophagus are increasing.[3] This year, pancreatic cancer surpasses breast as the third most common cancer killer[4] and by 2020 passes CRC as the second most common.[5] By 2030, hepatoma may overtake CRC as the third deadliest cancer.[5] Currently, most upper GI cancers present symptomatically at a late stage and are among the most lethal cancers.[6] These alarming trends are calls for action.

Effective early detection methods are needed desperately. However, with a few exceptions,[7] screening for upper GI cancers in most countries has not been pursued because of the relatively low prevalence of cancers at individual sites and lack of cost-effective screening tools.

Disclosures: Mayo Clinic has licensed technology to Exact Sciences related to the commercialized stool DNA test Cologuard. As co-inventor of licensed technology, Dr D.A. Ahlquist shares royalties to Mayo Clinic according to institutional policy. Funding provided by Carol M. Gatton endowment.
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Gastroenterol Clin N Am 45 (2016) 529–542
http://dx.doi.org/10.1016/j.gtc.2016.04.009 **gastro.theclinics.com**
0889-8553/16/$ – see front matter

This overview briefly examines molecular approaches as potential screening solutions to the challenge of GI cancer. It summarizes the types of molecular markers being considered, gives examples of molecular tools under development, and appraises the future role of molecular methods for universal detection of GI cancers. Although there are obvious implications on downstream endoscopic evaluation and management, these important clinical aspects are not addressed.

MECHANISMS, MEDIA, AND MARKERS

The concept of molecular screening is based on measurement of tumor-derived markers in readily accessible media. The promise of this approach lies in its ease for patients and potential to open doors for cost-effective screening of multiple GI cancers with a single test. Several key biological and technical elements must come together for molecular screening to be feasible. First, markers must reliably enter and remain in the target medium to be detectable at earliest cancer stage and, ideally, with precancer. Second, assays with sufficient technical sensitivity are needed to detect tumor markers in low abundance. And, third, highly discriminant markers must be identified that are positive when a GI neoplasm is present but otherwise remain negative, and such markers would ideally also predict the anatomic site of the primary GI tumor. Fueled by rapid technical advances, there is intense academic interest in this approach and increasing development by industry.

With GI cancers there exists the unique opportunity for noninvasive screening by marker detection either in blood or, because of their shared property of luminal exfoliation,[7] in stool. A central obstacle with blood testing has been the difficulty detecting earliest stage cancer and precancer. Tumor markers are detected readily from circulation with later stage cancer, but are often below detection limits with stage I cancers and precancers.[8,9] In contrast, CRC and precancerous polyps exfoliate molecular markers abundantly into stool.[8,10,11] A direct comparison between stool and plasma testing of DNA markers in paired samples showed substantially higher marker levels and diagnostic yield with stool than with plasma (**Fig. 1**A), which prompted a conceptual model suggesting that the biological mechanism of marker release by exfoliation favors early stage detection over that by vascular invasion (**Fig. 1**B).[8] It may be possible to overcome the biological constraints of limited vascular invasion in early stage disease by exploiting potential alternative mechanisms of marker entry into blood, such as by release of exosomes (nanovesicles emitted from surface of tumor cells and containing proteins, RNA, and DNA)[12] or phagocytosis by circulating macrophages, or simply by improved analytical sensitivity to detect the associated low plasma levels of tumor markers. With stool testing, it is unclear how effectively markers exfoliated from upper GI tumors can be recovered after traversing the digestive gauntlet. Model systems suggest that the small quantities of cells estimated to be shed from upper GI tumors can be detected in stool using sensitive techniques,[13] and pilot case-control studies have demonstrated that it is possible to detect tumor markers in stool from patients with known upper GI cancer.[14,15]

A comprehensive summary of specific candidate tumor markers is beyond the scope of this clinical review. The major classes of markers include intact tumor cells and cellular constituents including proteins, RNA, and DNA; each class has diagnostic advantages and disadvantages.

Whole Tumor Cells

Intact tumor cells may be recovered from the circulation. Sophisticated sequencing and other assay methods are now available to determine the genomic makeup