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Review

Oncotype DX® colon cancer assay for prediction of recurrence risk in patients with stage II and III colon cancer: A review of the evidence

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ABSTRACT

Advances in molecular biology have enabled identification of tumor biomarkers that allow for individualized risk assessment for patients with cancer. Molecular predictors of clinical outcome can help inform discussion regarding the role of adjuvant chemotherapy in patients with resected colon cancer, such as those with stage II colon cancer in which the benefit of adjuvant therapy is controversial or those with stage III colon cancer who may have a lower risk of recurrence and less absolute benefit from oxaliplatin therapy. This article summarizes the data surrounding the development, validation, and clinical and economic utility of the Oncotype DX® colon cancer assay, a multigene expression assay validated to independently predict recurrence risk in patients with stage II and III colon cancer beyond traditional factors.

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Introduction

Colorectal cancer remains the third leading cancer and the third leading cause of cancer death in both men and women in the United States, despite advances in treatment. There were over 130,000 new cases and over 50,000 deaths from colorectal cancer in 2014 alone [1]. The mainstay of treatment for non-metastatic

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colon cancer is surgical resection of the tumor with adequate lymphadenectomy [2]. While surgery alone can be curative in 70% of patients with localized (stage II & III) colon cancer, a proportion of patients eventually develops tumor recurrence and ultimately dies of metastatic disease. Since surgeons are the main physicians of contact after tumor resection, we are challenged to answer questions regarding prognosis and need for further multi-modality treatments. Surgeons are furthermore responsible for making the decision to refer patients to medical oncologists for consideration of adjuvant chemotherapy.

However, the benefit of adjuvant chemotherapy in resected stage II colon cancer remains controversial, and identifying which patients might derive the greatest benefit from adjuvant therapy for resected stage III disease is difficult. Biomarkers that can accurately assess the disease recurrence risk of an individual patient and better discriminate the absolute treatment benefits are needed. Specifically, it would be especially valuable to reliably identify stage II patients who are at higher risk of recurrence to have a greater absolute benefit with the addition of adjuvant chemotherapy; and it would be useful to stage III patients who are at lower risk for recurrence and may have less absolute benefit from oxaliplatin therapy to be spared its associated toxicity. Indeed, with advances in genomic medicine, several multigene assessment platforms are available today to help provide such information. The Oncotype DX® colon cancer assay, a 12-gene colon cancer assay, has been commercially available worldwide since 2010 and is the most established colon platforms available [12,13]. It was developed similarly to the multigene assay, Oncotype DX® Breast Cancer Assay (Genomic Health, Inc., Redwood City, CA), that has become part of the standard of care in breast cancer management, and has a well-established role in management guidelines published by the NCCN, St. Gallen Consensus, NICE, and the American Society of Clinical Oncology [8–11]. The purpose of this review article is to summarizing the development of and the clinical data validating this assay for the quantitative assessment of recurrence risk in the setting of colon cancer adjuvant-treatment. We also highlight potential uses of this assay in surgical practice for coordination of post-surgical recommendations, as well as the economic implications of its use.

Existing considerations in adjuvant chemotherapy for colon cancer

In patients with stage II colon cancer, adjuvant chemotherapy is currently being offered to patients considered to be at higher risk for disease relapse based on clinicopathologic factors, as they are presumed to derive greater benefit from adjuvant therapy. The National Comprehensive Cancer Network (NCCN) guidelines include a wide range of acceptable management strategies for stage II colon cancer: observation, single-agent fluoropyrimidine chemotherapy (i.e., 5-fluorouracil with leucovorin (5-FU/LV) or capecitabine), combination chemotherapy with oxaliplatin, and enrollment in clinical trials [2]. The guidelines recommend that treatment decisions about adjuvant therapy consider treatment benefits and risks, patient preferences, clinicopathologic features of high risk of systemic recurrence, and mismatch repair (MMR) status. High risk features have conventionally included tumor-stage 4 (T4) disease, low number of lymph nodes removed, bowel obstruction or perforation, lymphovascular invasion (LVI), positive or close margin status, high tumor grade, and perineural invasion [2]. In contrast, patients with tumors that are MMR-deficient (MMR-D) may have a good prognosis and do not appear to benefit from 5-FU chemotherapy [3].

Among these prognostic features, identification of T4 stage and MMR-D status are most helpful in defining risk for patients with stage II colon cancer. Each of these factors helps identify approximately 15% of stage II patients at either end of the spectrum of recurrence risks. In the remaining approximately 70% of T3, MMR-proficient (MMR-P) patients with an average risk of recurrence, tumor grade, LVI and perineural invasion fail collectively to provide quantitation of recurrence risk. Furthermore, the determination of these histopathologic risk factors can be subjective and incomplete [2,4], while their combined use in a treatment algorithm has not been prospectively validated. These limitations of traditional histopathologic markers of risk underscore the need for new tools that allow surgeons to more accurately differentiate high-from low-risk patients with stage II colon cancer following tumor resection.

For patients with stage III colon cancer, surgical resection followed by combination chemotherapy with 5-FU/LV plus oxaliplatin is the current standard recommendation [2]. Adding oxaliplatin to conventional fluoropyrimidine chemotherapy results in an approximate 20% relative risk reduction for disease-free survival (DFS), amounting to a 6% absolute benefit after 5 years. In addition, an exploratory analysis from the MOSAIC trial showed a trend toward improved 5-year DFS in a subset of stage II patients with high-risk features who received oxaliplatin in addition to 5-FU/LV [5]. However, oxaliplatin is associated with significant toxicity, including a risk of long-term peripheral neuropathy [6,7]. Since the absolute benefit from added oxaliplatin-based adjuvant chemotherapy is uncertain in stage II disease and may vary considerably in stage III disease, but oxaliplatin carries a significant risk of toxicities, a newer method for defining the risk of disease relapse may help the medical oncologist chose 5-FU vs. oxaliplatin-based regimens.

Availability of molecular tools for risk stratification, together with intra-operative findings and clinicopathologic features, can help both the surgeon and the medical oncology team formulate an optimal and individualized approach to postsurgical care.

Methods

To identify literature utilized in this review, PubMed indexed literature was searched using key MeSH (Medical Subject Headings) Terms and Subheadings from the National Library of Medicine controlled vocabulary thesaurus used for indexing articles for PubMed. Only publications in English were considered. Searches were refined using the Advanced Search Builder. MeSH Terms/Subheadings used included, but were not limited to the following: Oncotype DX Colon, Colonic Neoplasms/drug therapy; Colonic Neoplasms/genetics; Colonic Neoplasms/mortality; Colonic Neoplasms/pathology; Gene Expression Regulation, Neoplastic; Neoplasm Recurrence, Local; Neoplasm Recurrence, Local/prevention & control; Predictive Value of Tests; Prognosis; Tumor Markers, Biological/analysis; Tumor Markers, Biological/genetics; Chemotherapy, Adjuvant; Chemotherapy, Adjuvant/economics; Cost-Benefit Analysis; Quality-Adjusted Life Years. The authors reviewed the identified manuscripts for relevance to the study.

Results

A total of 12 studies were identified that described the development, validation, and clinical and economic utility of the 12-gene assay (Table 1).

Development of the 12-gene colon cancer assay

The 12-gene colon cancer assay for estimating risk of recurrence was developed through quantitative reverse transcription-PCR on RNA extracted from fixed, paraffin-embedded tumor blocks from 4 large, independent cohorts of patients with stage II or III colon