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A Multigene Prognostic Assay for Selection of Adjuvant Chemotherapy in Patients with T3, Stage II Colon Cancer: Impact on Quality-Adjusted Life Expectancy and Costs

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ABSTRACT

Objectives: Uncertainty exists regarding appropriate and affordable use of adjuvant chemotherapy in stage II colon cancer (T3, proficient DNA mismatch repair). This study aimed to estimate the effectiveness and costs from a US societal perspective of a multigene recurrence score (RS) assay for patients recently diagnosed with stage II colon cancer (T3, proficient DNA mismatch repair) eligible for adjuvant chemotherapy. **Methods:** RS was compared with guideline-recommended clinicopathological factors (tumor stage, lymph nodes examined, tumor grade, and lymphovascular invasion) by using a state-transition (Markov) lifetime model. Data were obtained from published literature, a randomized controlled trial (QUick And Simple And Reliable) of adjuvant chemotherapy, and rates of chemotherapy use from the National Cooperative Cancer Network Colon/Rectum Cancer Outcomes study. Life-years, quality-adjusted life expectancy, and lifetime costs were examined. **Results:** The RS is projected to reduce adjuvant chemotherapy use by 17% compared with current treatment patterns and to increase quality-adjusted life expectancy by an average of 0.035 years. Direct medical costs are expected to decrease by an average of $2971 per patient. The assay was cost saving for all subgroups of patients stratified by clinicopathologic factors. The most influential variables affecting treatment decisions were projected years of life remaining, recurrence score, and patients' disutilities associated with adjuvant chemotherapy. **Conclusions:** Use of the multigene RS to assess recurrence risk after surgery in stage II colon cancer (T3, proficient DNA mismatch repair) may reduce the use of adjuvant chemotherapy without decreasing quality-adjusted life expectancy and be cost saving from a societal perspective. These findings need to be validated in additional cohorts, including studies of clinical practice as assay use diffuses into nonacademic settings.

Keywords: cancer, cost-effectiveness, cost-utility, health economics, technological change.

Introduction

Colorectal cancer is the third most common cancer in the United States, and the second leading cause of cancer mortality, resulting in 49,920 deaths in 2009 [1]. Based on estimates from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, an estimated 105,000 persons were diagnosed with colon cancer in 2010 [2]. At least one-quarter of new cases are stage II cancer (American Joint Committee on Cancer [AJCC] staging T3-T4 N0M0, Dukes' B2, tumor has grown into or through the outermost layers of the colon and may be attached or grown into other nearby tissues or organs [T3-T4], no regional lymph node [LN] metastasis [N0], no distant metastasis [M0]) [3,4].

Surgical resection is the cornerstone of management for patients with stage II colon cancer [3,5]. Because approximately only one-quarter are expected to experience a recurrence within 5 years of diagnosis, the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology guidelines state that the routine use of adjuvant chemotherapy (aCTX) for all medically fit patients is not recommended [3,5]. Guidelines recommend physicians to discuss with patients potential cure rates with surgery alone and the associated toxicities with aCTX [3].

Several clinicopathological characteristics have been identified as risk factors for disease recurrence and are commonly used to select patients for treatment. These include T4 tumor, bowel perforation, bowel obstruction, poorly differentiated tumor, lymphovascular invasion (LVI), and number of LNs examined [3,5]. The presence of deficient DNA mismatch repair (MMR) (or microsatellite instability high) is a favorable risk factor and may indicate reduced benefit from aCTX with fluoropyrimidine-only regimens [6].

In unselected patients, the potential benefit of aCTX in patients with stage II colon cancer (T3, proficient DNA MMR) is small. The QUick And Simple And Reliable (QUASAR) study was a

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randomized trial of fluorouracil and folinic acid (5FU/LV) compared with observation alone in patients with complete resection for colon or rectal cancer, no evidence of distant metastases, and uncertain benefit from adjuvant therapy based on physician assessment [7]. Chemotherapy resulted in an approximate 4% survival benefit at 3 years among all 3239 patients enrolled in the trial; the relative risk for recurrence with chemotherapy versus observation was 0.78 (95% confidence interval [CI] 0.64–0.95) [7]. The relative risk of recurrence for the 2146 patients with stage II colon cancer was 0.82 (95% CI 0.65–1.08). The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer study evaluated 2246 patients with stage II or stage III colon cancer after surgery for curative intent randomized to 5FU/LV plus oxaliplatin (FOLFOX) or 5FU/LV alone [8]. A subset analysis of the 899 patients with stage II cancer showed no difference in overall survival (hazard ratio = 1.00; 95% CI 0.70–1.41) and in disease-free survival (hazard ratio = 0.91; 95% CI 0.61–1.36). In an unplanned subgroup analysis, patients with high-risk features had a trend for improved disease-free survival (hazard ratio = 0.74; 95% CI 0.56–1.06) [9]. By inference, patients without high-risk features should have a trend toward worse disease-free survival with FOLFOX compared with 5FU/LV alone. The NCCN guideline states that FOLFOX is not considered as an appropriate therapy for patients without high-risk features [5]. The large variability in the use of aCTX, especially oxaliplatin-containing regimens, reported in the NCCN Colon/Rectum Cancer Outcomes study suggests that identifying patients at the greatest risk who might benefit from adjuvant treatment is a challenge [10].

Substantial interest exists in using gene-expression profiles to estimate prognosis and predict response to aCTX in stage II colon cancer [11]. A 12-gene reverse transcriptase-polymerase chain recurrence score (RS) assay (Genomic Health, Inc., Redwood City, CA) that quantifies the risk of recurrence in stage II colon cancer (0-lowest, 100-highest) was validated by prospective analysis of archived paraffin-fixed tumor tissue from 1436 patients with stage II cancer who participated in the QUASAR study [12]. The RS was found to be a statistically significant, independent predictor of recurrence risk ($P = 0.004$), disease-free survival ($P = 0.01$), and overall survival ($P = 0.04$) [12]. Other independent research groups have confirmed that the RS is an independent predictor of recurrence risk [13,14]. The specific aim of this study was to assess long-term patient outcomes and costs of the RS when used to guide the use of aCTX in "average-risk" (T3, proficient DNA MMR) stage II colon cancer compared with the prevailing use of traditional clinicopathological criteria.

Methods

Analytical Overview

The target population was defined as patients with stage II colon cancer who have undergone surgery in whom life expectancy and comorbidities do not preclude the consideration of aCTX. Patients with T4 tumor or the presence of deficient DNA MMR were excluded. We compared the RS for deciding the use of aCTX against current practice, which includes guideline-recommended clinicopathological characteristics that predict the risk of recurrence, for example, number of LNs examined (<12 or >12), LVI (yes/no), and tumor grade (high/low).

A state-transition (Markov) analysis was conducted to estimate a representative patient's life expectancy and quality-adjusted life-years (QALYs) with and without the RS (Fig. 1A). QALY was calculated by multiplying the time in specific health states (without recurrence and after recurrence) by corresponding health-related quality-of-life weights or utilities [15]. Utility weights for no recurrence, recurrence, and chemotherapy were derived from the relevant literature [16].

We obtained numbers of patients diagnosed with stage II colon cancer from SEER (National Cancer Institute) database, and computed percentages of patients by age. Median age was 69.5 (interquartile range 61.5–75.5) years.

The propensity of a patient to receive aCTX based on clinicopathological factors was derived from analyses published by Earle et al. [10] using the NCCN Colon/Rectum Cancer Outcomes Database. These multivariate analyses showed that the four most influential and statistically significant variables associated with propensity to prescribe aCTX were age, number of LNs examined, LVI, and tumor stage. The proportions of chemotherapy patients receiving different types of chemotherapy were extracted from this study and from surveys of medical oncologists [10,17].

By using estimates from the multivariate regression model published by Earle et al., we generated the propensity to receive chemotherapy as a function of years of life remaining, number of LNs examined, and LVI. Results are presented for patients with T3 lesions only, as T4 tumors are considered "high risk" and the use of adjuvant treatment is routine. We applied a polynomial approximation to the age covariate, which was analyzed as a bracketed variable in their regression, to obtain propensity to receive chemotherapy as a function of expected years of life remaining. The presence of LVI, fewer LNs examined, and younger age increased the propensity to receive chemotherapy.

By using the life-table methods described above, we computed the benefit with chemotherapy in life-years gained and QALYs gained as a function of years of life remaining a patient may expect if she or he does not have tumor recurrence. Recurrence rates are based on average for patients with T3 tumors. Relative risk reduction of chemotherapy is set to 0.18 as described in the main text. The benefit of chemotherapy increases for patients with longer expected years of life remaining (Fig. 2).

For the RS, a patient was assumed to receive aCTX if aCTX was expected to increase quality-adjusted life expectancy. The model estimates the difference between the QALY gained with aCTX for preventing recurrence (Q2; Fig. 1B) and the utility loss of aCTX's inconvenience and toxicities (Q3). A patient was assumed to receive aCTX if the difference was positive ($Q2–Q3 > 0$). The QALY gained corresponds with the risk of recurrence (derived from the RS) and the predicted years of life remaining for the patient if he or she had not been diagnosed with colon cancer. Therefore, the decision to receive aCTX is not based only on the RS, but also permits the consideration of other factors, such as years of life remaining and inconvenience/toxicities of aCTX. Given the same RS, more years of life remaining is associated with a higher Q2; hence, the propensity to recommend aCTX is higher. This assumption is consistent with current practice patterns reported by Earle et al. [10], where the propensity to prescribe aCTX is highest among younger patients.

Risk of Recurrence and Death

The 3-year risk of recurrence, based on results reported from the QUASAR validation study, varied between 10% and 26% for patients with T3 lesions [12]. The relative reduction in recurrence risk associated with aCTX, compared with observation alone, was set to 0.18, based on analyses reported for stage II colon cancer (T3, proficient DNA MMR) from the QUASAR study [7]. When applied to the 3-year recurrence risk with observation alone in patients with T3 stage II colon cancer with intact MMR, aCTX is estimated to reduce the recurrence risk at 3 years (i.e., absolute risk reduction) by an average of 3.2% (range 1.9%–5.2%).

The risk of mortality related to relapse of colon cancer was obtained from the SEER (National Cancer Institute) database [2]. Risk of death from causes not related to colon cancer was derived