Effect of Oncotype DX® Colon Cancer Test Results on Treatment Recommendations in Patients with Stage II Colon Cancer

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Background

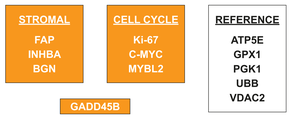
The Need for Validated Markers of Recurrence Risk in Stage II Colon Cancer

- The decision to use chemotherapy in stage II colon cancer is challenging.
  - There is a need to balance toxicity, risk of recurrence, and expected absolute benefit of treatment.
- Current guidelines recommend consideration of adjuvant chemotherapy for "higher risk" stage II patients based on clinical and pathologic factors.[1,2]
  - Evidence for these conventional risk factors is limited.
  - For the 75% of stage II patients who have T3N0, Mismatch Repair-Proficient (MMR-P) tumors, there are no informative markers to ascertain risk.
- There is a need for standardized, validated markers of recurrence risk to inform adjuvant treatment decision-making in stage II colon cancer, particularly for patients with T3N0 MMR-P tumors.

Development and Validation of the Oncotype DX Colon Cancer Assay in Stage II Colon Cancer

- The 12-gene colon cancer Recurrence Score® (RS) (Genomic Health, Inc., Redwood City, CA) assay was developed using data from 1,851 stage II/III patients in four large, independent studies conducted with the NSABP and the Cleveland Clinic.[3]
- The continuous 12-gene RS was validated as a predictor of recurrence risk in stage II colon cancer patients following surgery in two prospectively-designed studies using
  - 1,436 stage II colon cancer patients from the QUASAR clinical trial.[4]
  - 690 stage II colon cancer patients from the CALGB 9581 clinical trial.[5]
- The 12-gene RS has been commercially available since January 2010.
- To evaluate the impact of the Oncotype DX Colon Cancer Assay results on clinical practice in stage II colon cancer, it is important to examine its impact on adjuvant treatment recommendations.
  - This study is the first opportunity to assess the impact of the 12-gene RS on treatment recommendations through a survey of medical oncologists.

Figure 1. The 12-Gene Oncotype DX Colon Cancer Recurrence Score



RS =+ 0.15 x Stromal Group − 0.30 x Cell Cycle Group + 0.15 x GADD45B

Study Objective

- Characterize the impact of the Oncotype DX Colon Cancer Assay on adjuvant treatment recommendations in stage II colon cancer

Study Design

- A web-based survey was developed through cognitive interviews with four medical oncologists.
- Target population: U.S. medical oncologists who ordered Oncotype DX for three or more stage II colon cancer patients starting in January 2010, when the assay became commercially available.
- Each respondent was asked to focus on the single most recent stage II colon cancer patient for whom the Oncotype DX assay was ordered.
- The 34-item survey recorded
  - Patient's characteristics
  - Pre- and post-assay treatment recommendations
  - Oncologist's general practice patterns
- The survey was conducted from December 2010 to December 2011.

Methods

- The primary outcome measure was the total proportion of treatment recommendations that changed after the oncologists received the Oncotype DX colon assay results.*
- Changes in treatment recommendations were summarized according to treatment intensity
  - Increased intensity was defined as a change from observation to (any) chemotherapy or a change from non-oxaliplatin-containing to oxaliplatin-containing chemotherapy.
  - Decreased intensity was defined as a change from (any) chemotherapy to observation or a change from oxaliplatin-containing to non-oxaliplatin-containing chemotherapy.
- The practice setting and patient characteristics were summarized descriptively for all physicians who completed the survey.

*Calculated as ratio of the number of treatment recommendations that changed to the number of physicians who provided a treatment recommendation before receiving the Oncotype DX Colon Cancer Assay results

Study Population

- All 346 U.S. medical oncologists who ordered the Oncotype DX assay for three or more stage II colon cancer patients were contacted through mail and e-mail.
  - 139 accessed the survey online
    - 4 of whom were ineligible
    - 19 of whom did not complete the survey
- 116 eligible physicians completed the survey (34% response rate)
- The vast majority (86%) of physicians came from a community setting and had an average of 16 years in practice. Half of the oncologists saw more than 40 newly diagnosed colon cancer patients in a typical year (Table 1).
- Treatment patterns of the surveyed physicians were typical of those previously reported in stage II colon cancer.[6]
- Patient characteristics were representative of the contemporary stage II colon cancer population; >80% of patients had T3 tumors and ≥12 nodes examined (Table 2).

Table 1. Physician Practice Characteristics

	All (N=116)
Practice setting	
Academic	14 (12%)
Community	100 (86%)
Other	2 (2%)
Years in practice	
Mean (SD)	15.8 (9.1)
Median (range)	14.5 (2-40)
Number of newly diagnosed colon cancer patients in a typical year:	
Mean (SD)	54.8 (44.1)
Median (range)	42.5 (10-250)
Percentage of newly diagnosed colon cancer patients with stage II disease in a typical year:	
Mean (SD)	24.3 (13.7)
Median (range)	20 (5-60)
Among newly diagnosed colon cancer patients with stage II disease who were followed in a typical year:	
Percentage who underwent MMR/MSI testing	
Mean (SD)	52.3 (37.1)
Median (range)	50 (0-100)
Percentage treated with adjuvant chemotherapy:	
Mean (SD)	36.0 (18.8)
Median (range)	30 (0-95)
Of patients treated with adjuvant chemotherapy, percentage who received oxaliplatin-containing regimen	
Mean (SD)	66.2 (31.8)
Median (range)	75 (0-100)

SD, standard deviation; MSI, microsatellite instability

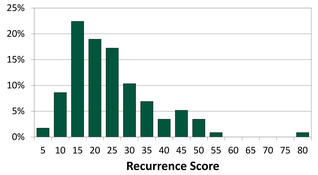
Table 2. Patient Characteristics

	All (N=116)
Age, years	
Mean (SD)	61.3 (11.8)
Median (range)	62 (32-85)
Tumor classification (T Stage)	
T3	94 (81%)
T4	22 (19%)
Number of lymph nodes examined	
<8	4 (3%)
9-11	15 (13%)
≥12	97 (84%)
MMR tested (n=76)	
MMR-D/MSI-H	13 (17%)
MMR-P/MSI-low	46 (61%)
Unknown	17 (22%)

Results

- Distribution of the 12-gene RS shifted towards lower values compared to that observed in the QUASAR validation study (median = 32)
  - This observation is consistent with lower RS values reported for the Oncotype DX Breast Cancer Assay in commercial datasets compared to clinical studies.[7]

Figure 2. Distribution of Recurrence Score Results



Statistic	RS Values
Mean (SD)	22.7 (12.1)
Median	20
25, 75 percentiles	14, 28
Min - Max	1-77

Impact of the Oncotype DX Colon Cancer Assay on Treatment Recommendations in Stage II Colon Cancer

- 92 (79%) of 116 evaluable physicians had a treatment recommendation before ordering the Oncotype DX Colon Cancer Assay (Table 3)
  - Most (52/92 = 57%) pre-assay treatment recommendations included chemotherapy.
- 27 (29%) of 92 treatment recommendations changed after the 12-gene RS was obtained
  - Treatment intensity decreased for 18 (67%) of these 27 treatment recommendations.
  - Treatment intensity increased for 9 (33%) of these 27 treatment recommendations.

Table 3. Pre- vs Post-Assay Recommendations (n=92)

Pre-Assay	Post-Assay (N)			
	Observation	Non-oxaliplatin chemotherapy	Oxaliplatin chemotherapy	Total
Observation	31	**4**	**5**	40
Non-oxaliplatin chemotherapy	**6**	13	**0**	19
Oxaliplatin chemotherapy	**8**	**4**	21	33
Total	45	21	26	92

RS led to increase in treatment intensity in 9 patients

RS led to decrease in treatment intensity in 18 patients

- The treatment intensity decreased more often for lower RS values (trend test p-value = 0.0035) (Table 4).

Table 4. Change in Treatment Intensity as a Function of RS Values

Treatment Intensity	RS Tertiles*			
	Low Tertile	Mid Tertile	High Tertile	Total
Changed	12 (39%)	9 (31%)	6 (19%)	27 (29%)
Decreased	10 (32%)	7 (24%)	1 (3%)	18 (20%)
Increased	2 (6%)	2 (7%)	5 (16%)	9 (10%)
No change	19 (61%)	29 (100%)	26 (81%)	65 (71%)
Total	31 (100%)	29 (100%)	32 (100%)	92 (100%)

* Definition of RS tertiles: Low RS < 16, Mid RS 16 ≤ RS <25, High RS ≥ 25

Strengths and Limitations

Strengths

- Relatively large study (>100 oncologists) with physicians' treatment patterns representative of contemporary US colon cancer medical practice
- One-third of all physicians invited to participate responded to the survey, comparable to response rates reported in the literature.[8]
- To minimize recall bias, physicians were instructed to retrieve patient charts on their most recent patient who received Oncotype DX when answering survey questions.
- To assure familiarity with the assay, target population included physicians who had used the test for three or more patients.

Limitations

- Retrospective exploratory survey which does not permit real-time assessment of the impact of RS results on treatment recommendations
- Physicians surveyed represented users of the Oncotype DX Colon Cancer Assay within the first two years of commercial availability which may include 'early adopters.'
- The survey focused on a single most recent patient which may or may not be representative of physician's practice.

Summary

- In this online survey, the impact of the 12-gene RS on treatment recommendations for stage II colon cancer patients in a real life clinical setting was assessed for the first time.
- Treatment recommendations were changed by RS results 29% of the time.
- Two-thirds of the changes resulted in decreased treatment intensity with changes from oxaliplatin containing chemotherapy to non-oxaliplatin containing chemotherapy and from (any) chemotherapy to observation.
- A significant trend of decreasing treatment intensity with lower RS values was observed.

Conclusions

- The results of this study suggest that the use of the RS may be associated with a meaningful change in treatment recommendations for stage II colon cancer patients.
- Use of the Oncotype DX Colon Cancer Assay may lead to reductions in treatment intensity, contributing to the assay's cost effectiveness.
- Studies are ongoing to prospectively investigate the impact of the Oncotype DX assay on clinical decisions and to evaluate cost effectiveness in clinical practice.

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