



Predicting disease recurrence in stage II colon cancer: expression signatures and other biomarkers

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Colorectal carcinoma is the second most common cancer in females and the third most common in males, with an estimated 1.4 million cases and 693,900 cancer-related deaths in the year 2012 (1). The incidence of colorectal cancer is highest in developed, industrialized countries, with a generally higher incidence for men than women in most countries. Prediction of prognosis and treatment decisions in this disease entity rely strongly on the tumor, node, and metastasis (TNM) classification for malignant tumors (UICC/AJCC), arguably the most well-established classification system worldwide (2). Whereas curative treatment can be achieved for most early stage cancers (UICC I) by radical tumor resection alone, advanced and metastasized cancer (UICC IV) requires aggressive multimodal treatment including cytotoxic therapy. However, therapy management is much less evident in stage II colon cancer patients, which comprise roughly a quarter of all colon cancer cases. By definition, stage II represents locally advanced tumors (T3-T4 N0 M0) that have not spread to locoregional lymph nodes. The overall 5-year survival for this subgroup of colon cancer patients is around 75–80% (3). Current guidelines recommend surgical tumor resection only, and a generalized adjuvant treatment with its well-known systemic side effects is not recommended for this tumor stage (4,5). Despite radical surgical tumor resection, a sizeable proportion of stage II patients develop post-operative disease relapse, in the form of distant metastasis to the liver or lungs, or local recurrence. Unfortunately, the return of the disease in these “high-risk” patients leads to death in most cases, despite systemic therapy. However, the current 7th edition of the TNM system

does not allow accurate prediction of prognosis in stage II colon cancer, and more reliable and precise biomarkers are awaited urgently (6). Currently, the risk factors defined by the guidelines involve clinical factors such as an insufficient number of resected lymph nodes, T4 stage, bowel perforation or obstruction (4,5). The application of reliable prognostic factors and the precise estimation of the individual recurrence risk of a patient holds the potential to improve treatment decisions in daily clinical practice. Considerable attempts have been made by many groups to achieve reliable patient stratification for disease recurrence in stage II colon cancer. The current hypothesis is that biomarkers could allow specific stratification for disease-recurrence, allowing more aggressive treatment for high-risk patients which would otherwise not receive multimodal therapy. Different approaches have been chosen, ranging from protein-based approaches that quantify enzymatic activity of cell-cycle regulator CDK1, or protein expression and phosphorylation (7,8). Moreover, genetically defined approaches such as integrative analysis of molecular genetic markers has been shown to be superior to current clinical risk factors (9), and differential expression of miRNAs has been shown promising (10). Gene-expression signatures based on microarray analysis have also been tested successfully, among them the test kits ColDx and ColoPrint (11-15). The litmus test for clinical acceptance for any biomarker is its feasibility for use on formalin-fixed, paraffin embedded tissue (FFPE), and a thorough test on independent patient collectives. Several of the above described biomarkers have so far only been tested on fresh-frozen tissue samples, which have the advantage of excellent

preservation of proteins and nucleic acids, but require a sophisticated infrastructure that may not be available in many clinics worldwide. A recent report by Donna Niedzwiecki and colleagues demonstrates the successful application of a gene-signature based biomarker, the ColDx test, on a large cohort of FFPE samples from stage II colon cancer (16). The ColDx signature had been tested previously on FFPE-tissue on an independent collective (11). The authors were able to utilize tissue a large and well-documented retrospective patient cohort from a clinical trial that tested the use of the therapeutic antibody Edrecolomab, which targets the glycoprotein EpCAM on the cell-surface. Whereas the original phase III trial failed to prove a beneficial effect of the therapeutic antibody, Niedzwiecki and her co-workers put the archived tissue samples to good use and tested the ColDx expression signature. Despite technical problems, likely due to long storage of the archived tissue blocks, the expression signature could be tested on n=393 patients (16). Risk stratification by the ColDx signature classified 55% of the collective (216 of 393) as “high risk”. Among these, 62 recurrence events (29%) were recorded, as opposed to 29 events in the 177 “low risk” group (16%). Importantly, the authors report that the ColDx test provided significantly greater prognostic value for the recurrence-free time interval than established clinical markers, such as patient age, number of examined lymph nodes, and DNA mismatch-repair status. Moreover, the ColDx test was retained as a significant prognostic factor independent of established clinical risk factors in a multivariable model. The “high-risk” patients, as defined by the ColDx test, had a probability of being recurrence-free at 5 years of 82% (95% CI of 79% to 85%), as opposed to a recurrence-free survival rate of 91% (95% CI of 89% to 93%) for the “low-risk” group of patients (16). Of note, the authors report that there was only minor overlap with an independent recurrence score, based on a 12-gene signature that had been tested on a subset of the same patient samples previously (13). Therefore, one may conclude that the various gene signatures presently determine different subgroups, regarding their tumor biology and disease progression. The use of any of the newly proposed biomarkers is certainly not feasible as “stand-alone” marker for clinical treatment decisions in the near future, but there is high potential for these biomarkers to be incorporated alongside traditional clinical risk markers to achieve an individualized prognosis for every patient. However, the question arises what clinical consequence would result from a “high-risk” test result of a well-defined

biomarker. The “high-risk” group of patients might receive adjuvant chemotherapy (e.g., a FOLFOX/CAPOX regime) in addition to surgical treatment to prevent disease relapse, whereas “low-risk” patients could be spared the toxicity of the systemic therapy. However, there is still scarce evidence that high-risk patients would actually benefit from adjuvant chemotherapy (17). Moreover, the “high-risk” group of the ColDx test comprised 216 patients, out of which 154 did not develop disease relapse. Therefore, the amount of “over-therapy” would be reduced as opposed to treatment of all stage II patients, but could still be regarded as considerable. Further, it remains to be seen whether tests like the ColDx are not only prognostic, but also predictive for response to adjuvant therapy. Nonetheless, recent advances in the field of targeted therapies for other solid tumors demonstrate that stratified therapies for defined subgroups of patients are feasible, and may be also be applicable in for colon cancer. Patient stratification based on biomarkers that allow the evidence-based use of novel targeted therapies, in concert with established treatment modalities like surgery and chemotherapy, may offer significant survival benefits with greatly reduced side-effects for future patients.

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