An 18-gene signature (ColoPrint) for colon cancer prognosis

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ColoPrint is an 18-gene expression signature designed to predict disease relapse in patients with early-stage colorectal cancer (CRC). We discuss the potential impact of ColoPrint on clinical practice, and its contribution to our knowledge of CRC molecular heterogeneity.

Many oncologists are familiar with MammaPrint (Agendia, Amsterdam, The Netherlands) and Oncotype DX (Genomic Health, Redwood City, CA, USA), two multi-gene assays used to predict disease relapse and guide adjuvant therapy decisions in patients with early-stage breast cancer. Recently, both companies have published gene-expression classifiers for predicting disease relapse in early-stage colorectal cancer (CRC).[1,2] Here, we discuss the potential clinical and scientific impact of one of these classifiers – ColoPrint (Agendia).

CRC is the third leading cause of global cancer mortality. Outcomes for patients with early-stage CRC are heterogeneous, with five-year survival rates ranging from 72% to 83% in stage II disease and from 44% to 83% in stage III disease.[3] In the past two decades, randomised trials have demonstrated a survival advantage for patients treated with surgery and adjuvant chemotherapy,[4] particularly those with stage III disease. However, in these trials, many patients were cured by surgery alone, suggesting that it might be possible to omit chemotherapy in selected patients. Clinical guidelines currently recommend observation for stage I disease and adjuvant chemotherapy with a combination of a fluoropyrimidine and oxaliplatin for those with stage III disease.

In stage II CRC, the benefit of adjuvant chemotherapy is contentious, with ASCO recommending the integration of clinical risk criteria to select patients for adjuvant therapy.[5] Identifying molecular markers that can inform therapeutic decisions, such as the need for treatment and type of adjuvant therapy, would be tremendously useful. To address this challenge, Salazar et al.[1] analyzed fresh-frozen tumour tissues from 188 patients with stage I to IV CRC using Agilent gene-expression microarrays. By correlating the expression of more than 40,000 genes with metastasis-free survival, they identified an optimal set of 18 genes that was used to construct the ColoPrint prognostic classifier. In an independent validation series of 206 patients with stage I to III CRC, 60% of patients were classified as 'low risk', with a five-year relapse-free survival (RFS) rate of 87.6%. The remaining 40% 'high-risk' patients exhibited a RFS rate of 67.2% (HR=2.5; 95% CI 1.33–4.73; P=0.005). In multivariate analyses, ColoPrint remained one of most significant prognostic factors (HR=2.69; P=0.003), and in stage II CRC, ColoPrint was superior to the ASCO criteria for the assessment of cancer recurrence risk (HR=3.34; P=0.017). The authors concluded that, compared with conventional clinicopathological criteria alone, ColoPrint provides more accurate information on the risk of recurrence and may facilitate selection of low-risk patients who can be spared chemotherapy.

While these results are encouraging, it

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is prudent to interpret them in the context of an early discovery study. Several gene-expression classifiers for predicting CRC relapse have been described,[6,7] but none have achieved clinical utility. It is worth noting that studies relying on fresh-frozen tissue (for example ColoPrint) typically have modest sample sizes and cannot benefit from archival material collected from randomised clinical trials. As a comparison, Oncotype DX (colon), the parallel CRC prognostic classifier developed using formalin-fixed paraffin-embedded tissues, was tested in more than 1800 patients from four adjuvant trials.[2] Therefore, further retrospective validation of ColoPrint in large independent cohorts is clearly required. Fortunately, a prospective study, PARSC (Prospective study for the Assessment of Recurrence risk in Stage II Colorectal patients using ColoPrint) has already been initiated to evaluate the performance of ColoPrint in the classification of patients in the clinical setting.[8]

The potential for gene signatures to influence treatment decisions depends on the disease stage. Molecular markers are most likely to impact the management of stage II disease, where the need for adjuvant chemotherapy is already based on assessment of clinical risk features. Molecularly, microsatellite instability (MSI) status is a marker of good prognosis in patients with stage II CRC and may be associated with a lack of benefit from adjuvant fluoropyrimidine therapy.[9] Indeed, most MSI high (MSI-H) patients were identified as 'low risk' by ColoPrint. However, the 48% discordance observed between ColoPrint and the ASCO clinical risk criteria[1] suggests an additional discriminative value of ColoPrint beyond clinical characteristics. Stage II patients identified as 'low-risk' by ColoPrint exhibited an excellent five-year survival similar to that seen for stage I disease, raising the possibility that ColoPrint may identify stage II patients for whom chemotherapy can be avoided. That said, we must remember that good prognosis does not necessarily mean lack of benefit from adjuvant therapy. For example, Oncotype DX (colon) has not been shown to be predictive in stage II CRC, despite its prognostic significance.[2] Further studies should also be performed to establish if ColoPrint is purely prognostic or whether it is predictive of treatment benefit as well.

In stage III CRC, adjuvant chemotherapy is the standard of care. In our opinion, oncologists are highly unlikely to omit chemotherapy altogether in medically fit patients with stage III CRC unless the data supporting excellent prognosis in molecularly low-risk patients is very compelling. The study by Salazar et al.[1] cannot address the role of ColoPrint in stage III disease, since there were only 62 patients with stage III disease and there was a trend towards inferior RFS in high-risk patients (P=0.1). Nevertheless, a validated prognostic signature for stage III CRC patients might still be useful to identify low-risk patients for whom oxaliplatin chemotherapy might be omitted and who might be treated with a fluoropyrimidine alone. Moreover, with the exception of oxaliplatin, stage III CRC has demonstrated notable failures for drugs that were efficacious in the metastatic setting, such as bevacizumab, cetuximab and irinotecan. Given the curative intent of treatment in stage III CRC and the vast investment into these completed trials, it might be fruitful to search for molecular markers predictive of selective benefit for therapies that otherwise do not provide an advantage in an unselected population.

The present study also broadens our knowledge regarding the inherent molecular heterogeneity of CRC.[1] Using unsupervised clustering techniques, three molecular subgroups were identified that had different survival outcomes. These groups were differentially enriched for *BRAF* activating mutations and MSI-H, suggesting unique underlying biologies. Notably, only the largest subgroup (n=110) was used to develop the prognostic signature. Given the distinct biological makeup of these three groups, it is plausible that the prognostic impact of ColoPrint is specific to the biological subgroup from which it was developed, analogous to the questionable prognostic value of Oncotype DX in HER2-positive breast cancer.[10] Salazar et al.[1] do not provide prognostic information of ColoPrint in the three biological subgroups – this should also be addressed in a future study. Investigations addressing the relationship of ColoPrint to other molecular markers (for example, 18q loss of heterozygosity, *KRAS* mutation status and CpG island methylation subtypes) are also warranted.

In conclusion, Salazar and colleagues are to be commended for their promising findings that ColoPrint might provide additional prognostic information beyond clinicopathological criteria in early-stage CRC. We eagerly await the results of the ongoing clinical trial seeking to prospectively validate ColoPrint.

Details of the references cited in this article can be accessed at www.cancerworld.org

Practice point

In colorectal cancer, novel molecular markers such as gene-expression signatures offer the potential of improving upon current prognostic models that are based on clinical criteria. However, widespread acceptance of these markers will necessitate identifying opportunities where they directly influence clinical management decisions.

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