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Editorial

Mismatch Repair as a Prognostic Marker for Adjuvant Therapy in Colorectal Cancer – How Soon is Now?

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Treatment for colorectal cancer is guided principally by stage in a classification that has changed little over 70 years. Patients presenting with stage II and III resected colorectal cancer have no detectable metastatic disease, but a proportion of these patients will have undeclared micrometastatic disease, which it may be possible to eradicate with adjuvant treatment.

Adjuvant chemotherapy with 5-fluorouracil (5-FU)-based regimens was the standard of care for the treatment of stage III patients [1–3] and a modest benefit of oxaliplatin has been shown [4,5]. These studies also included high-risk stage II patients, but with a lower risk of relapse, even similar hazard ratios translate into small clinical benefit and the role for adjuvant chemotherapy remains debatable [6–8]. The largest study (QUASAR) suggested possible benefits of adjuvant chemotherapy of the order of 3–4% in overall survival for stage II patients [9], although of only marginal statistical significance. CALGB9581 (albeit investigating immunotherapy in this setting) confirmed the good prognosis of many patients with low-risk, stage II colorectal cancer [10].

Despite numerous emerging biomarkers, decisions on the potential benefits of adjuvant chemotherapy in stage II disease have used subjective analyses of adverse histopathological features (derived from the initial adjuvant 5-FU studies without subsequent validation). The hope is that biomarkers will allow better resolution of the heterogeneity thought to be present in colorectal cancer and, subsequently, more effectively targeted treatment. We believe there is now a strong case for routinely assessing mismatch repair (MMR) status in stage II colorectal cancer.

A Fork in the Road – Different Pathways to Colorectal Cancer

DNA MMR was first identified through the discovery that some colorectal tumours showed variations in 'microsatellites', mononucleotide and dinucleotide repeats [11]. These tumours were less likely to feature mutations in *p53* and *KRAS*, less likely to be invasive and more likely to occur proximally, suggesting an alternative to the classic model suggested previously by Fearon and Vogelstein [12] of tumours developing through loss of APC function and activation of *KRAS* [13]. Subsequently it became clear that deficient MMR (dMMR) was responsible for this 'microsatellite instability' ('MSI' or 'MSI-H'). Germline mutations in MMR proteins were found to be the driving mechanism behind tumours seen in Lynch syndrome (hereditary non-polyposis colorectal cancer). A similar phenotype of colorectal cancers with MSI is seen in a proportion of sporadic colorectal cancers with either a somatic mutation in MMR proteins or more commonly gene silencing through promoter methylation [14].

MMR status (dMMR or proficient [pMMR] corresponding to MSI-H or microsatellite stability, respectively, see Figure 1) can be determined by direct analysis of MSI (polymerase chain reaction analysis) or by immunohistochemistry for the MMR proteins (MLH1, MSH1, MSH6 and PMH2). With high sensitivity (92.3%) and specificity (100%) [15,16], immunohistochemistry is cheaper and simpler than polymerase chain reaction analysis, and provides a simple and effective means of establishing MMR status that is deliverable in a conventional setting. Specifically, the absence of immunohistochemical staining for one or more of these proteins implies dMMR (i.e. MSI-H).

Strong Evidence of a Prognostic Effect

There has been growing evidence that dMMR status is a strong prognostic biomarker for improved outcomes in

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Mismatch repair status	Abbreviation		Microsatellite status	Abbreviation
Deficient (loss of staining for MLH1, MSH1, MSH6 or PMH2)	dMMR	=	Microsatellite instability (detectable via polymerase chain reaction)	MSI or MSI-H
Proficient	pMMR	=	Microsatellite stable	MSS

Fig 1. Terminology.

colorectal cancer (Table 1). A meta-analysis in 2005 derived a pooled hazard ratio of 0.65 for overall survival in favour of dMMR (95% confidence interval 0.59–0.71) from 32 studies comprising 7642 patients [17]. This advantage held for stage II and III patients, with a pooled hazard ratio of 0.67 (95% confidence interval 0.58–0.78). A subsequent 2010 meta-analysis found an increased overall survival for dMMR patients from 20 studies comprising 9243 patients with stage I–IV disease [18]. This result was also seen in an analysis of the subset of 10 studies of stage II and II colorectal cancers with an odds ratio for survival at completion of study follow-up of 0.65 (95% confidence interval 0.53–0.79, $P < 0.0001$). Similar results were seen in the studies where data were available for disease-free survival.

Retrospective analysis of 1913 patients enrolled into QUASAR showed this prognostic effect of dMMR in stage II colorectal cancer, highlighting the association with clinical features [19]. Twenty-six per cent of right-sided tumours were dMMR as opposed to 3% of left-sided tumours and 1% of rectal cancers. dMMR rates were twice as frequent in stage II as opposed to stage III tumours (12% versus 6%). Crucially dMMR tumours showed about half the recurrence risk of their pMMR counterparts, with a recurrence rate of 11% in dMMR versus 26% in pMMR tumours (risk ratio 0.53, 95% confidence interval 0.40–0.70; $P < 0.001$).

Similar results have recently been published from a population-based series from a single institution in Norway [20]. Complete data were available for 613 patients undergoing curative resection for stage II colorectal cancer. Fourteen per cent of cases were dMMR (defined by polymerase chain reaction for MSI), more frequently seen in women (19%) and right-sided tumours (29%). Although outcomes were worse that seen in the QUASAR clinical trial cohort, MSI-positive (dMMR) stage II cases had significantly improved 5 year relapse-free survival.

Does Mismatch Repair Status Predict Response to 5-fluorouracil?

Beyond the prognostic effect there are accumulating data that MMR status is predictive of the response to adjuvant chemotherapy (Table 2), where dMMR tumours may not derive benefit from 5-FU and indeed may do worse. Mechanistic data support a role for dMMR tumours exhibiting resistance to 5-FU [25]. Clinical data are derived from adjuvant trials or cohort studies [17,18,24], although large numbers of patients are needed to amass the numbers of

Table 1
Studies reporting mismatch repair status as a prognostic marker in stage II and III colorectal cancer

Reference	Design	Number of stage II and III	Prognostic marker	Notes
[17]	Meta-analysis	2935	Yes HR = 0.67 for OS (95% CI 0.58–0.78) in dMMR	
[18]	Meta-analysis	4014	Yes OR = 0.65 for survival at end of study (95% CI 0.53–0.79) in dMMR, $P < 0.001$	
[21]	Retrospective from RCTs	457	Yes HR = 0.46 for DFS (95% CI 0.22–0.95) in dMMR, univariate analysis, $P = 0.03$	Benefit not maintained in multivariate analysis
[22]	Prospective in RCTs	1852	Yes HR = 0.77 (95% CI 0.71–0.80) for OS in dMMR, $P = 0.029$	
[19]	Retrospective from RCTs	1913	Yes RR = 0.53 (95% CI 0.40–0.70) for recurrence in dMMR, $P < 0.001$	
[23]	Retrospective cohort	787	Yes HR = 0.40 for OS at 3 years (95% CI 0.19–0.86) in dMMR, $P = 0.001$	Calculation includes stage I and IV patients
[20]	Retrospective cohort	613	Yes HR = 1.60 for RFS (95% CI 1.01–2.52) in pMMR, $P = 0.045$	Result due to stage II rather than stage III, analysis included stage I

RCT, randomised controlled trial; HR, hazard ratio; RR, risk ratio; OR, odds ratio; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair.