Focusing the management of rectal cancer

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Comment on: Sebio A, Salazar J, Páez D, *et al*. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015;15:77-83.

Abstract: Rectal cancer treatment has undergone major changes over the last 15 years with a focus on individualized care based around MRI assessment of the relationship of the tumour to the mesorectal fascia, improved surgical techniques and targeted use of pre-operative oncological therapies in patients with locally advanced disease. The recognition that some tumours responded completely to pre-operative chemoradiotherapy, and the selective use of a non-operative policy has led to a quest to further identify those patients and their tumour in whom this approach could be used, irrespective of MRI stage. With no clear patient factors identified, the tumour and its gene expression has become a target for research to identify individual single-nucleotide polymorphisms, which may indicate a response to specific treatment, or not. To date some agents have been identified and trialed, such as cetuximab, with individual tumours being assessed for response allowing directed treatment. The reviewed paper by Sebio and colleagues report a study that links polymorphisms in the DNA repair gene XRCC1 with response to neoadjuvant 5-Fluorouracil treatment in rectal cancer patients. However, genetic heterogeneity alone may not explain the variations of drug response and environmental factors may lead to epigenetic effects and therefore alter responses. Therefore whilst this study demonstrates the impact of different single nucleotide polymorphisms (SNPs), it is only one step forward, but perhaps a step in the right direction.

Keywords: Rectal cancer; genomics; tumor heterogeneity; single nucleotide polymorphisms (SNPs)

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Over the last 15 years, there has been a change in the focus of therapy for rectal cancer. Traditionally surgery was the mainstay of treatment, either with removal of the rectum and restoration of bowel continuity (anterior resection) or removal of the rectum and anus and formation of a colostomy (abdominoperineal excision). Prior to the introduction of MRI staging of rectal cancer and the planning of individualised care through the multidisciplinary team (MDT), the principle concern was the avoidance of an incomplete resection, technically an involved circumferential resection margin (CRM +ve) as this is associated with high levels of local recurrence (1-3).

The recognition that pre-operative chemoradiotherapy in selected cases and the resultant down-staging of disease through MRI-directed care has led to improvements in overall survival and a reduction in CRM +ve rates (4). However, the morbidity of surgery remains and the potential for lifelong alteration of bowel function, through low anterior resection syndrome (LARS) or a permanent colostomy persists following surgery and impairs quality of life (5).

It was the recognition of the work of Dr. Habr-Gama in Brazil and the non-operative management of rectal cancer following chemoradiotherapy that has led to a

desire to identify patients who may respond completely to chemoradiotherapy and hence avoid surgery, known as "*Watch and Wait*" (6). Rates of complete clinical response (cCR) (and radiological response) have been reported as high as 15% in selected series of advanced disease in the UK and across cancer networks, however, there is also a group of patients who undergo resection and there is no evidence of tumour remaining in the specimen—a pathological complete response (pCR) (7,8). Together these may make up 25% of tumours selected for CRT based upon MRI-stage. The challenge currently is to identify these patients, as no characteristics or biochemical markers have been identified for cCR/pCR. In many centres around the world for early stage tumours CRT is avoided if there is no evidence of a potentially involved CRM and surgery is offered. This contrasts with the Habr-Gama group who offered CRT to all low rectal tumours, and achieved higher rates of cCR. The question is who best to treat with CRT irrespective of MRI stage?

There are no current biomarkers to predict the response of patients to this highly variable treatment. An accurate method for predicting the response to CRT would therefore allow for improved treatment choice with avoidance of unnecessary side effects: patients with chemoradiation-resistant disease would be spared the morbidity of this treatment. Equally, patients with a prediction of pCR may be spared radical surgery and its complications. Individualised genomic sequencing assessing for genetic mutations that could act as predictive biomarkers to cancer treatment offers a future potential for individualised therapy. Single nucleotide polymorphisms (SNPs), which are variations of one nucleotide occurring across the genome, are the most frequently identified mutations (9). In their recent paper, Sebio *et al.* explored specific SNPs in epidermal growth factor receptor (EGFR) ligands and DNA repair genes in rectal cancer patients with the aim of identifying potential biomarkers of treatment response (10).

EGFR, which is a trans membrane tyrosine kinase receptor, has been extensively studied as a biomarker in several malignancies. Activation of EGFR leads to a cascade of cellular events that promote cell proliferation, invasion and metastatic spread. Aberrant activation of EGFR may be achieved by several mechanisms including SNPs. The work of Khambata-Ford and colleagues established that the expression levels of EGFR ligands (AREG and EREG) can be predictive for cetuximab efficacy in patients with colorectal cancer (11). Further studies were able to confirm the predictive value of the ligands in cetuximab treated patients in colorectal cancer. Yet, the role of EGFR ligands in rectal cancer under different chemotherapeutic regimens, as the authors point out, has not been studied.

Additionally, CRT exerts its effects through generating DNA damage. Therefore, genetic variants of DNA repair genes in the form of SNPs could modulate treatment response. A recent large pharmacogenetic analysis examining 66 SNPs showed that there is an association between SNPs in DNA repair genes and response to neoadjuvant CRT in patients with locally advanced rectal cancer (12). Sebio *et al.* report studies that link polymorphisms in DNA repair gene XRCC1 with response to neoadjuvant 5-Fluorouracil treatment in rectal cancer patients (10).

The best regimen for neoadjuvant treatment in rectal cancer however, is not yet fully established, due to lack of consistent differences in terms of local recurrence between different regimes (13). Whilst short course radiotherapy (SRT-5 Gy per day for 5 days) has been adopted as the standard neoadjuvant treatment in some countries, in others long-course CRT (45–50.4 Gy over 5 weeks with concomitant chemotherapy) is preferred. Other regimes have used induction chemotherapy prior to CRT, for example the expert trial and added cetuximab in follow-up arms (Expert-C) (14,15). However, DNA repair gene pathways and EGFR alterations differ depending on the treatment chosen. Additionally, literature on SNPs in EGFR ligands in the context of treatment of rectal cancer with capecitabine only, is lacking. Sebio *et al.* address this by selecting SNPs in previously unexplored ligands in patients treated with neoadjuvant capecitabine for rectal cancer, making this a novel study (10).

The authors analysed 28 known polymorphisms in 84 patients with locally advanced rectal cancer. They found an association between three SNPs and pCR after neoadjuvant CRT with capecitabine (10). The associations were tested in both uni-variate and multi-variate regression models. Two SNPs retained their significance, one located in DNA repair gene (ERCC1) and one in EGFR ligand (AREG). The identification of the rs11942466 C>A polymorphism in the AREG gene region, previously found to be correlated with outcome in metastatic CRC, is a novel finding in rectal cancer studies. Previous studies looking at SNPs in ERCC1 in rectal cancer failed to establish any associations, yet, the authors have established a significant association between RCC1 rs11615 C>T and pCR. They attribute this to the effect of the capecitabine on DNA repair pathways that differs from other chemotherapy agents used in previous studies.

There are, however, limitations to this paper. The study was under-powered to show significant differences in association and important outcomes. The short follow-up period also affected association links with recurrence rates and overall survival outcomes. The authors acknowledge these limitations. Patient related factors such as sex, age and comorbidities, may influence response to targeted therapies. Patients in the study were not stratified into different age groups and potential gender differences were not explored. These factors should be considered as important predictive biomarkers. Nevertheless, the authors succeed in shedding a light at new associations between SNPs in rectal cancer and treatment response. The SNPs identified could potentially be explored further as biomarkers of treatment response and would benefit from replication in large cohorts, or through tissue banks of rectal cancer specimens who have outcome data for recurrence and survival, particularly the pCR group and those in whom there is disease progression despite CRT.

Moreover, the molecular heterogeneity of rectal cancer is believed to be one of the factors responsible for the variability in treatment response among patients with the same stage of cancer (16). Tumour heterogeneity refers to the differences between tumours of the same type in different patients, or between cancer cells within the same tumour. Both can lead to different responses to therapy, even targeted therapy. This may explain why some tumour cells remain present in the patient after completion of cancer treatment. Therefore, single biopsy specimens of primary tumours may not represent the full genetically diverse malignant picture. Similarly, analysis techniques may not be sensitive enough to detect the lower frequency changes in tumour sub clones.

Finally, there is an increasing consensus that genetic heterogeneity alone is not enough to explain variations in drug response between different individuals. The influence of the environment and interaction of genes with environmental variables, represented by the field of epigenetics, has been the focus of research in the last decade. Epigenetic mechanisms modify gene expression independently of DNA sequence (17,18). They can be environmentally induced, tissue specific and can have similar effects to pathogenic mutations: they can silence, increase or decrease the expression of a gene. Epigenetic mechanisms currently play an important role in development, prognosis and treatment response of colorectal cancer and are becoming more prominent in rectal cancer research. With that, an emerging need to combine genetic and epigenetic data is arising.

Current selection of CRT is based upon MRI-staging, which is attempting to ask the question for the surgeon, "if I operate will I achieve a CRM negative specimen?" This is a crude tool, CRT being used in advanced stage cases or those with poor MRI-prognostic features; however, Habr-Gama has demonstrated that CRT in all low rectal tumours achieves a higher rate of cCR, yet at the expense of increased use of CRT. Therefore the improved understanding of the biology within an individual tumour within an individual patient remains the goal for treatment selection. No crude biomarkers, such as NLR ratio, CEA, age, sex, etc. have offered an accurate selection, perhaps identification of SNPs will offer the way?

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Burton S, Brown G, Daniels IR, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer 2006;94:351-7.
2. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ 2006;333:779.
3. Quirke P, Durdey P, Dixon MF, et al. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986;2:996-9.
4. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014;32:34-43.
5. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg 2012;255:922-8.

6. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004;240:711-7;
7. Dalton RS, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis 2012;14:567-71.
8. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174-83.
9. Preskill C, Weidhaas JB. SNPs in microRNA binding sites as prognostic and predictive cancer biomarkers. Crit Rev Oncog 2013;18:327-40.
10. Sebio A, Salazar J, Páez D, et al. EGFR ligands and DNA repair genes: genomic predictors of complete response after capecitabine-based chemoradiotherapy in locally advanced rectal cancer. Pharmacogenomics J 2015;15:77-83.
11. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230-7.
12. Boige V, Vincent M, Alexandre P, et al. DPYD Genotyping to Predict Adverse Events Following Treatment With Flourouracil-Based Adjuvant Chemotherapy in Patients With Stage III Colon Cancer: A Secondary Analysis of the PETACC-8 Randomized Clinical Trial. JAMA Oncol 2016. [Epub ahead of print].
13. Biondo S, Fraccalvieri D, Golda T, et al. Update on advances and controversy in rectal cancer treatment. Tech Coloproctol 2016;20:145-52.
14. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010;11:241-8.
15. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620-7.
16. Bettoni F, Masotti C, Habr-Gama A, et al. Intratumoral Genetic Heterogeneity in Rectal Cancer: Are Single Biopsies representative of the entirety of the tumor? Ann Ann Surg 2017;265:e4-e6.
17. Virani S, Bellile E, Bradford CR, et al. NDN and CD1A are novel prognostic methylation markers in patients with head and neck squamous carcinomas. BMC Cancer 2015;15:825.
18. Goel A, Boland CR. Epigenetics of colorectal cancer. Gastroenterology 2012;143:1442-1460.e1.

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