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EDITORIAL

Or why translational research is vital for the future treatment of rectal cancer

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«How doth the little crocodile
Improve his shining tail…» *(Alice in Wonderland)*

The past 20 years have seen remarkable clinical improvements in the management of locally advanced rectal cancer. Increasing standardisation of meticulous surgery, sophisticated novel preoperative radiotherapy techniques and the integration of chemotherapeutic agents have all led to improvements in local control although with minimal impact on overall survival (OS). Significant challenges still remain, with 10–40% of patients still requiring a permanent stoma, the high risk of metastatic disease and prediction of response to chemoradiation (both absence and complete response) being high on the agenda. So strategies to preserve the sphincters whilst maintaining good anal function and quality of life, optimisation of integration of systemic chemotherapy and prediction of local response to chemoradiation are among the tests required for the next decade.

Presently standardised techniques in magnetic resonance imaging (MRI) of the rectum have allowed a radiological definition of rectal cancer whereby the possibility of surgery completely removing the disease can be shown preoperatively [1, 2]. From this a categorisation of risk based on MRI and clinical staging can be developed as follows:

1. Low risk (cT1-cT2, some cT3a, crm– N0)
2. Locally advanced (cT3bcd, some T4 crm–/N+)
3. Potentially unresectable advanced (cT3 crm+ or cT4)
4. Unresectable disease (extension to lateral pelvic sidewall/lateral pelvic lymph node involvement/disease outside the pelvis)

MRI imaging and review of the surgical specimen has also led to the identification of other important factors including proximity to the circumferential resection margin (CRM) in millimetres, N-stage, extramural vascular invasion (EMVI) and perineural invasion (PNI), all of which are relevant to the risk of local recurrence and the development of metastatic disease.

Yet, currently, the tumour–node–metastasis stage (obtained either clinically by MRI or histologically at surgery) is the only proven prognostic marker to aid in the identification of patients with aggressive patterns of disease. K-ras testing can define groups of patients, who may not benefit from EGFR inhibition in the palliative setting, but has no accepted role in chemoradiation.

What can we do to continue improving our treatment whilst taking into account the changing landscape in terms of long-term consequences of treatment and OS? An obvious answer is that better understanding of the tumour biology both on a molecular and cell biology level is essential. Chemoradiation consists of the integration of chemotherapy into a radiation schedule with the view that radiation dose can be reduced and hence less morbid (though with the same benefit), and the systemic chemotherapy will treat micrometastatic disease. An improved understanding of the effects of these agents on the tumour cells and microenvironment might offer significant long-term benefit.

The paper in this journal, "Molecular changes consistent with increased proliferation and invasion are common in rectal cancer", by R. Hughes, the late J. Parry, J. Beynon and G. Jenkins [3], attempts to determine the impact of neoadjuvant therapy on changes in induced gene expression. Identification of biological predictors of tumour response to preoperative therapies is an obvious area of investigation. A predictive biomarker can offer information about the effect of a particular therapeutic intervention and can also predict differential efficacy of a particular therapy according to the marker status guiding the choice of therapy, identifying optimum drug doses and predicting toxicity.

The majority of current aspirations in rectal cancer chemoradiation have concentrated on integration of new chemotherapeutic and biological agents. Relatively little thought has been given to the radiation component. Ionising radiation works by the development of oxidative moieties that damage DNA and nucleic acids as well as a number of cytoplasmic targets. The molecular consequences of this action include repair of DNA – predominantly by homologous recombination but with associated cessation of cell-cycle progression and apoptotic and mitotic cell death. The proteins involved in these processes are well characterised and understood but

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have been little investigated in rectal cancer *in vivo* or *in vitro*.

As we acknowledge above, the response of tumours to radiotherapy is sometimes poorer than expected, and the late effects on normal tissues are significant. Radiosensitivity is strongly influenced by a multiplicity of biological factors and in the future we need to characterise and target the biological basis for such individual differences. Resistance particularly is likely to originate from host characteristics, pharmacogenomics and the ability to repair DNA damage. These factors are all highly individual and to date elude our ability to predict them accurately.

Recent strategies have looked further at the integration of biological agents and combination chemotherapy with a backbone of radiotherapy. The majority of work has concentrated on the epidermal growth factor receptor pathway, which is targeted by a number of agents. Antibodies to the receptor itself (cetuximab and panutunumab) have been shown to be effective in improving disease-free survival (DFS) and OS in patients with advanced, metastatic colorectal cancer, albeit in a situation where a number of 'downstream' factors are favourable. A logical progression has been to integrate these agents into rectal chemoradiation, a strategy that has, to date, been fruitless.

Examination of this downstream pathway has shown the crucial role of K-Ras and, more recently, B-Raf in this pathway. As an understanding of this pathway develops, the reasons why attempts to integrate these molecularly targeted agents into chemoradiotherapy of rectal cancer have been unsuccessful become clearer with the supposition that inhibition of external signals that drive cell cycle progression might lead to cell cycle arrest in a radioresistant part of the cell cycle.

We have generated some hypotheses. Inhibition of apoptosis as a means of predicting local recurrence and failure to respond to radiochemotherapy is an area that shows some promise. Examination of the role of survivin and caspase 3 shows that these important proteins have contradictory effects in rectal cancer [4–6]. Survivin is an unfortunately named protein encoded by the *BIRC5* gene and functions as an inhibitor of caspase activation, thus preventing apoptosis. Survivin is not expressed in terminally differentiated tissue but is highly expressed in tumour and foetal tissues. Overexpression of survivin correlates with a diminished response rate and an early rate of local recurrence.

In comparison with survivin, caspase 3 is involved in the execution phase of apoptosis and expression correlates with increased apoptotic activity. Overexpression of Caspase 3 is associated with improved pCR rates and DFS. Measurement of these proteins' pretreatment offers an attractive means of tumour response prediction but, of course, also poses other, generally more interesting, questions such as what to do in a tumour that overexpresses survivin.

A glaring problem with this area is the failure of any concerted, international strategy to assess and understand the biology of rectal chemoradiation. There is, however almost an overabundance of small studies. On PubMed the term "rectal cancer and predictive factors" raised 622 papers. One research group has published 5 separate small studies on 8 different predictive factors with a minimum of 33 and a maximum of 57 patients from phase I/II studies. However, these factors have been examined separately with no attempt to combine them.

The limitations of such research is that these small studies have considerable heterogeneity, since the selection of patients, initial method of staging, the cytotoxic drugs used in CRT, the regimens, the duration and the dose intensity, the radiotherapy dose and fractionation all vary. There is also poor agreement about techniques and definitions, and hence reproducibility of these assays. In addition, we have information on the biological activity of only the primary tumour and not the mesorectal and pelvic lymph nodes, which may well respond differently.

Perhaps one of the most perplexing thoughts about rectal cancer is our current inability to form a cohesive strategy to look at the biology of the disease. At the time of writing there have been more than five major randomised phase III studies in chemoradiation looking at standard vs. experimental treatments with over 2000 patients treated and, presumably, the collection of 2000+ surgical specimens. This represents an enormous treasure trove of biological material for which a systematic approach (similar to that seen with PETACC3) [7, 8] to aspects of rectal cancer biology is needed.

If our ultimate goal is to use all the agents at our disposal (both cytotoxic and biological) to enhance rates of tumour downstaging, local control and survival, and identify the most active regimens that could eventually potentially obviate the need for radical surgery in selected patients, then we need biomarkers. Once we do have a convincing hypothesis regarding a biomarker, it will probably need to be validated in larger retrospective studies and independent cohorts. Finally, we will need to confirm with randomised prospective clinical trials. Perhaps for all the above reasons, it is not surprising that we have very little novel to offer in rectal cancer at the present time, but the current phase III trials have an obligation to collect tissue and perform translational studies.

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