How MRI became the Gold Standard in Rectal Cancer

Abstract
With the acceleration and ever increasing costs of technologies across the imaging modalities, any imaging technique proposed for improving the assessment of disease needs to undergo rigorous validation. Imaging validation is only accepted as a clinical gold standard if a priori assessment criteria are clearly defined before testing and then needs to be proven to be reproducible. Objective comparison by multivariate analysis against known standards and other clinical parameters enables the true added value of new techniques to be measured. Finally, for a staging method or technique to achieve acceptances as a gold standard - prospective validation of predefined imaging criteria against clinically relevant outcomes such as disease free survival, overall survival and local recurrence is also necessary. The development and acceptance of high resolution MRI for assessment of patients with rectal cancer illustrate how such validations can lead to changes in practice.

By the mid1990s, the Stockholm phase III randomised trials were showing a benefit in survival through the use of preoperative therapy in rectal cancer pelvic recurrence rates of 40% were being halved through pelvic radiotherapy(1). In the next generation of trials, selecting patients for preoperative radiotherapy was based on digital rectal examination of the "fixity of tumour" to identify high risk patients and by using endorectal ultrasound to identify early stage tumours for
avoidance of radiotherapy(2-4). At the same time, total mesorectal excision (TME) surgery was gaining wider acceptance and attention to surgical technique through subspecialisation was proving effective at reducing local recurrence rates(5, 6). The TME procedure required sharp dissection beyond the fascia propria of the rectum (the mesorectal fascia) to produce a rectal specimen surrounded by an envelope containing local tumor spread and deposits in an intact package. This was highly effective at substantially reducing local recurrence related to tumour deposits left in the pelvis - in the non TME trials of the 1990s pelvic recurrence rates of 30-40% were reported, these were more than halved through improvements in surgery(7). The work of Quirke et al showed that the relationship of tumour to the edge of the resected specimen formed by the mesorectal fascia in TME specimens was significantly associated with outcomes(8). The concept of visualising the mesorectal fascia and documenting the relationship of tumour to this was not yet appreciated. However, the advent of pelvic phased array coils and improved scan times afforded by fast spin echo T2 weighted sequences in the late 1990s provided an opportunity to evaluate images using resolutions hitherto only achievable using endorectal methods but with greater patient comfort and tolerance, better pelvic coverage and consequent improvements in anatomic detail - the mesorectal fascia and the anatomic compartments of the pelvis could now be understood(9-11). Over the ensuing years, MRI became a global standard of care for the primary evaluation of rectal cancers; the work progressed initially by first defining and correlating surgical and histological anatomy(12), developing MRI definitions and interpretation criteria based on precise ex vivo tissue and histological matching with high resolution MR images(11, 13-15). The focus was for staging of the primary tumour extent and lymph node spread but with greater understanding of pelvic anatomy, assessment could also determine the potential to resect tumour with clear margins. By prospective comparisons with the histological gold standard it was possible to prove that high resolution MRI improved accuracy compared with existing alternative methods and showed that MRI had significant clinical and cost benefits over traditional methods of preoperative stratification for therapy(16). Lymph node staging criteria in rectal cancer which had hitherto been based on measuring the
diameter was also questioned and from prospectively designed studies - was proven to be an inaccurate and unreliable means of assessing the likelihood of malignancy when compared with border and signal characteristics visible using high resolution methods(17). Scrutiny of the high resolution images revealed yet more prognostic information that had not previously been appreciated(18). One of the most important imaging biomarkers of tumour aggression is extramural venous invasion. This had not previously been assessed by imaging techniques yet was prevalent in 30-40% of patients and significantly associated with the development of distant metastases and local recurrence and, in the era of TME surgery, was significantly more prognostically important than lymph node status(19-21). In 2002, MRI was still not a global standard of care for assessing rectal cancer mainly due to uncertainties about the reproducibility of accurate MRI reporting by radiologists since good results had only been achieved in single centre studies. So, the multicentre international multidisciplinary research group for clinical investigations in rectal cancer (the MERCURY group) was established with research support funding from the Pelican Cancer Foundation(22). The group comprising : motivated specialist gastrointestinal radiologists engaged in multidisciplinary patient care who were able to undertake and submit high resolution protocol scans using proforma based standardised reporting of rectal cancer; TME surgeons willing to submit consecutive data for scrutiny and excellent pathologists prepared to routinely photograph, audit and standardise the pathologic assessment of TME specimens. The enthusiasm for the project from multidisciplinary colleagues led by Professor Bill Heald, Brendan Moran and Professor Phil Quirke and others ensured active recruitment from participating centres. A series of one day MRI teaching workshops succeeded in standardising radiology interpretation amongst 11 European centres and over the following two years, this multicentre multidisciplinary study accrued 428 patients and, with over 5 years follow up, provided comprehensive patient outcome data. The study demonstrated accurate and reproducible prediction of surgical resectability and prognosis(23, 24) and also showed that MRI mesorectal fascia involvement by tumour (defined as tumour at 1mm or less to the mesorectal fascia) significantly predicted for circumferential margin involvement and local
recurrence; now a target for future improvements in local treatment\cite{25, 26}. The study was adopted to the UK national trials portfolio in 2003 and the MRI training workshops became an established part of a government funded National TME development training programme that enabled MRI to become the standard and mandatory staging procedure for all patients with newly diagnosed rectal cancer\cite{27}. In 2012, the work of the MERCURY group was incorporated into national guidelines for staging and management of rectal cancer and into the design of current and future phase II/III clinical trials\cite{NCRI}. Elsewhere in Europe - similar impacts were seen and similar training initiatives were developed. The MERCURY study showed that low rectal cancers had significantly higher involved margin rates, the single most important cause of preventable pelvic recurrence in patients with rectal cancer. Analysis of the MRI data identified preoperative staging factors that could predict a high risk of positive margins in low rectal cancer\cite{28-37}. As a consequence, a staging model was developed to describe the anatomical and surgical planes for low rectal cancer which could improve outcomes by selective planning of radical surgery and the type of chemoradiotherapy\cite{37}. These are now being prospectively tested in the multicentre MERCURY II: low rectal study\cite{ESCP}. Once again, the UK department of health supported the dissemination of these advances as an English national training initiative and development programme for multidisciplinary colorectal cancer teams through the national "LOREC" programme delivered by the Pelican Cancer Foundation\cite{38}. Analysis of patient outcomes by MR stage for: local recurrence rates, disease free survival and overall survival has shown that avoidance of preoperative radiotherapy is safe in patients with MRI defined good prognosis tumour, confirming the ability of MRI based staging criteria to select patients who have good outcomes (3% local recurrence) with primary surgery alone\cite{39}. The technique allowed stratification of patients and better targeting of preoperative therapy thereby avoiding unnecessary morbidity from overtreatment\cite{39}.

The pursuit of validating imaging prognostic factors in rectal tumours with outcomes data remains a strong priority. Patients with MRI defined poor prognosis rectal cancer are at high risk of disease recurrence despite standard chemoradiotherapy and optimum surgery - so if improvements are to
be made in patient survival such information should be used to stratify treatment. Recently published outcome data have shown a promising gain in outcomes for MRI identified high risk patients given induction chemotherapy (40-43). This work has led to the identification of key imaging predictors of patients at risk for developing metastatic disease. These predictors are now forming the basis for patient selection with targeted treatments in several phase II/III trials in colorectal cancer (http://clinicaltrials.gov/). Highly selective strategies are more likely to yield positive trial results that will benefit high risk patients.

As a consequence of the MRI rectal trials, the trial workshops and assessment of quality of reporting, a need for standardisation of radiology cancer reporting has been highlighted. This is now being taken forward with the National Cancer Intelligence Network (NCIN) and the Royal College of Radiologists; the UK CASPAR initiative attempts to show that cancer reporting standards can be improved nationally with the use of synoptic reporting templates and similar initiatives are also being successfully piloted in Ontario and other healthcare systems (44).

Establishing any imaging technique as a "gold standard" is a significant challenge that requires stepwise validation and multidisciplinary collaboration if it is to succeed. Any new imaging biomarker will need to follow the logical principles now formally set out by REMARK if wider acceptance is to be achieved. The principles followed in the development of imaging biomarkers can be summarised as follows:

1. development of objective criteria from validation against known gold standards - a priori objective thresholds (rather than post hoc analyses) and clear definitions that can be prospectively applied to other populations.

2. quantification of the added value of a new technique by direct comparison with the existing best standards of assessment
3. multivariate assessment to determine whether a technique holds independent significance when compared against other more traditional standards

4. prospective validation of predefined criteria and techniques against clinically relevant outcomes

5. demonstration that any such technique can be taught and readily reproduced to achieve wider clinical acceptance

6. embedding into clinical trials and clinical practice with resulting measurable improvements in patient outcomes

References


