Novel radiation techniques – a personalised approach for patients with rectal cancer

Arthur Sun Myint,1 Vidhya Sagar Ramani,2 Amir Montazeri,1 Kate Perkins,1 Robert Myerson,3 and Jean Pierre Gerard.4 On behalf of the ICONE Group (International Contact Radiotherapy Society).

1. Clatterbridge Cancer Centre, Bebington, Wirral, United Kingdom.
2. Premion, Wesley Radiation Oncology, Brisbane, Australia.
3. University of Washington, St Louis, Missouri, United States of America.
4. Centre Antoine Lacassagne, Nice, France.
Email: sun.myint@clatterbridgecc.nhs.uk

Abstract

Surgery remains the standard of care for most rectal cancer as it offers the best chance of cure. However, for patients with early stage low rectal cancers there are several treatment options available using novel radiotherapy techniques. Good responders to novel radiotherapy can avoid surgery. Poor responders need salvage surgery. Patient selection is important and careful assessment after preoperative chemoradiotherapy can identify good responders, even with advanced rectal cancers. Restaging magnetic resonance imaging scans can identify good radiological responses, which need to be confirmed by clinical examination and endoscopy. A watch and wait policy can be adopted for good responders, with surgery avoided or deferred. A boost with contact radiotherapy or brachytherapy can be offered to elderly patients to improve local control. This treatment strategy needs to be evaluated via clinical trials, for which the contact x-ray and transanal endoscopic microsurgery trials have been set up. In this way a personalised approach can be offered for patients with rectal cancer using novel radiotherapy techniques.

Colorectal cancer is the third most common cancer worldwide in men (663,000 cases, 10% of total) and the second in women (517,000 cases, 9.4% of the total). Almost 60% of the cases occur in high resource regions, with the highest rate being estimated in Australia and New Zealand, where more than 14,000 new cases are diagnosed and over 4000 deaths occur each from the disease. As the ageing population increases, colorectal cancer in high resource countries could pose a major burden on health care costs.

About a quarter present with early stage (Stage 1),1 and 25% have metastatic disease at presentation.2 Seventy five per cent of cases are operable, however curative resection can only be carried out in 60% of cases.3 The standard of surgical care is total mesorectal excision. However, there is considerable morbidity and mortality associated with this for elderly patients. In addition, there are wide variations in the number of cases that require abdominoperineal resection (APR) across the surgical practice for small, early stage low rectal cancers, which is clearly unacceptable.4 With an increasingly ageing population, not all patients diagnosed with rectal cancer will be fit for surgery. In addition, initiatives such as the National Bowel Screening Program for Australians who turn 50, if successful, are likely to identify even more early rectal cancers, but not all patients who are fit will agree to extirpative surgery that involves a stoma.

Staging investigations using MRI are now mandatory for rectal cancer and those with threatened circumferential resection margins will be offered preoperative chemoradiotherapy.5 A proportion of these cases will not have any residual disease at the time of surgery. So far, despite concerted efforts using sophisticated translational research, reliable and reproducible molecular biomarkers to predict patients who can achieve pathological complete response have not been discovered. Post treatment MRI staging may identify good responders following treatment and it may be possible to defer major surgery in those who wish to avoid it.6 Novel radiotherapy techniques can improve local control in such cases without added toxicity and should be considered for the elderly and those medically not fit for extirpative surgery.7

Contact x-ray brachytherapy for small early rectal cancer (<3cm T1N0M0)

Contact x-ray brachytherapy, also called ‘Papillon’ technique after Professor J. Papillon who popularised this,7 has been used to treat selected patients with small, early stage rectal cancer for the past 80 years. The main advantage of contact x-ray brachytherapy (topical radiotherapy) is its ability to target the tumour directly, with minimal damage to the normal surrounding tissue. It uses low energy x-rays (50 KV), which penetrate only a few millimetres (dose falls to 60% at 5mm depth). At each treatment tumour cells are destroyed layer by layer. Therefore, underlying normal tissues are not damaged. Contact x-ray brachytherapy uses a very high dose of radiation (30 Gy) so the tumour cell kill is proportionally higher.8 Although the physical dose is 30 Gy, the biological equivalent dose is much higher (~45 Gy external beam equivalent). The treatment is given every two weeks -
allowing preferential recovery of normal tissue compared to tumour cells. The clinical response after two fractions can be used to differentiate between good responders and poor responders. Those who respond well after two fractions will continue with contact x-ray brachytherapy for a total of four treatments (total tumour dose 110 Gy). Figure 1 shows the typical evolution of changes seen during the treatment course of a responder to contact radiation. External beam radiotherapy (25 Gy/5#/5days) or chemoradiotherapy (45 Gy/25#/35days) can be offered to those with partial response, with the option to reassess response before extirpative surgery. If there is evidence of small residual tumour (<2cm) after radiotherapy, local excision such as transanal endoscopic microsurgery (TEMS) can be considered. If the response to radiotherapy is poor, it is important to proceed with extirpative surgery within eight to ten weeks after treatment. The feasibility of this approach has been evaluated in the ongoing CONTEM-2 (CONtact and Transanal Endoscopic Microsurgery) trial, which is an observational study set up by the ICONE (International Contact Radiotherapy Society) group.

**HDR brachytherapy for more advanced tumours (>3cm T1/T2/T3a N1 M0)**

More advanced rectal tumours >3cm should be treated with external beam chemoradiotherapy initially to downstage and downsize the tumour. The response following treatment should be assessed. High dose rate (HDR) brachytherapy can be offered to those with residual tumours, which are still visible or palpable. This will treat deeper residual tumour with a higher radiation dose. Contact x-ray brachytherapy delivers maximum radiation dose on the surface, whereas HDR brachytherapy also delivers radiation dose to deeper structures. Watch and wait policy can be offered to those who achieve complete clinical response. TEMS can be offered to those with minimal residual disease <2cm. The value of HDR brachytherapy boost was evaluated in a phase 3 randomised Danish trial comparing HDR rectal boost following chemoradiotherapy with external beam chemoradiotherapy alone. This has shown benefit for brachytherapy boost in terms of increased pathological complete response rates and microscopically clear resection margin (R0) rates in T3 rectal tumours.

**Figure 1:** Typical response to contact x-ray brachytherapy in a responder. Image A shows findings at first treatment session for a patient with T1N0 low rectal tumour. Image B shows findings two weeks later at the second session with only a minimal change in appearance. Image C shows further response at the third treatment session. Almost complete resolution at the time of the fourth treatment session as illustrated by image D. Images reproduced from Sun Myint et al. (in press).
The value of contact x-ray brachytherapy (Papillon) was evaluated in the Lyon 96-02 French trial and has demonstrated increased sphincter preservation (76% v 44%) in favour of Papillon boost.\textsuperscript{12} The updated long-term results presented at the European Society for Radiotherapy and Oncology meeting in 2011 confirmed the initial conclusions.\textsuperscript{13} The feasibility of this approach has been evaluated in the CONTEM-3 trial, which is an observational study set up by the International CONtact radiotherapy (ICONe) group for elderly and younger patients not keen on having a stoma.

**Watch and wait policy for clinical complete response? (T3/T4 - N1/N2 M0)**

Approximately 15-20% of patients will achieve complete response following preoperative chemoradiotherapy for advanced rectal cancer. Regardless of the response, most of these patients, will be offered radical surgery, as planned prior to their pre-operative treatment. There are several publications on the long-term data on these patients who are regarded as good responders showing improved recurrence free survival and overall survival.\textsuperscript{14,15} The question is how to identify these patients before planned surgery. Multidisciplinary teams recommend restaging MRI to assess the response. However, the majority of surgeons are reluctant to change the type of surgery that has been planned prior to treatment (eg. APR for low rectal cancer <6cm) regardless of the response.\textsuperscript{16} A recent publication from the Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study group on MRI response following chemoradiotherapy suggests that good responders can be identified prior to surgery (figure 2). Those who achieve complete pathological or near complete pathological response have better long-term outcomes than poor responders.\textsuperscript{6} Therefore, a less aggressive management approach can be adopted for good responders, with deferral of extirpative surgery when the patient has achieved a complete clinical response. There are some concerns about microscopic sub-mucosal residual disease in these apparent complete clinical responders, where MRI may not be able to pick up small volumes of residual malignant cells.\textsuperscript{17} These patients can be offered contact x-ray brachytherapy (Papillon) or topical radiotherapy to sterilise the residual cancer cells. A randomised trial, CONTEM-4, will address the role of contact boost in improving the outcomes for the good responders.

**1.4 HDR brachytherapy or contact x-ray brachytherapy as a retreatment**

Second malignancy in the pelvis is now increasingly recognised in patients who have had prior radiation treatment for carcinoma of the cervix, bladder or prostate cancer. These patients are usually offered extirpative surgery for their second malignancy. APR has to be offered even for small early stage low rectal cancers. Contact x-ray brachytherapy can be offered as an alternative for small low rectal cancer. If there is small residual tumour after contact x-ray brachytherapy, local excision or TEMS can be carried out. HDR brachytherapy can be used for more advanced tumours in the upper rectum that require preoperative radiotherapy for circumferential resection margin involvement. Due to the unique properties of

---

**Figure 2: Wait and watch policy for complete responders.** Pre treatment MRI (Ai) and endoscopy (Aii) of a patient who subsequently showed complete clinical response to neoadjuvant chemoradiation as assessed by interval MRI (Bi) and endoscopy.

- **Complete clinical response**
  - pre treatment MRI
  - pre treatment endoscopy
  - complete endoscopic response
  - no residual tumour
brachytherapy, the radiation dose to the closest previously treated tissues will be lower, which helps reduce the damage caused by repeated or re-irradiation.\textsuperscript{13}

**Implications**

The standard of surgical care in rectal cancer is total mesorectal excision. However, the mortality and morbidity from radical surgery is considerable, especially high in elderly and medically compromised patients. The mortality for a patient above the age of 80 years is 14% and 25% for those above 90 years.\textsuperscript{18} Morbidity such as delayed wound healing (20%), para-stomal hernias (30%) and anastomotic leakages (10%) is much higher with surgical surgery.\textsuperscript{19} The proportion of cases presenting with early stage rectal cancer in Australia is expected to increase in the next decades due to the introduction of colorectal screening. Despite detection of early stage disease, the gold standard surgical treatment for low rectal cancer is APR with permanent colostomy. This is an over-treatment as some cases can be cured with less aggressive surgical treatment. There is a national trial known as Transanal Endoscopic Microsurgery and Radiotherapy in Early Rectal Cancer (TREC) trial addressing this issue in the UK. For most patients, general anaesthetic is necessary even for local excision such as TEMS. For those patients who are not fit for general anaesthetic, contact radiotherapy or brachytherapy can be offered as an alternative treatment. Although the cure rates are not as high as radical surgery, there is lower mortality and morbidity.\textsuperscript{20} Patients should be fully aware of the treatment options that are available. All new cases should be discussed by the colorectal multidisciplinary teams. The outcome of the decision made at the multidisciplinary team should be conveyed to the patient by the clinician in charge and a plan of management mutually agreed. The patient’s choice should be taken into consideration as they may accept a higher oncological risk treatment option to avoid a stoma. If there is doubt, complex cases should be referred to specialised centres with experience so their access to best possible treatment is not compromised.

**Outlook**

Radical surgery should be avoided in elderly patients with early stage small low rectal cancer (T1NO0), as the mortality and morbidity is high.\textsuperscript{19} Contact radiotherapy can be offered as an alternative treatment option. The response to treatment can be assessed immediately after treatment and major surgery can be avoided for good responders. Poor responders should be offered immediate salvage surgery. Partial responders can be offered local excision using TEMS. A small proportion of patients (approximately 20%) with more advanced low rectal cancers (T3 N1 M0) could achieve complete clinical response after a course of chemoradiotherapy and the patients could be offered to adopt a watch and wait policy as part of a clinical trial. Those with more advanced tumours (T2/T3a N0M0) who are elderly can be treated with a similar approach as part of a clinical trial (CONTEM-3). Their long-term outcome is not compromised, however careful follow-up is necessary to detect recurrences.\textsuperscript{21} As the treatment options are complex, they should be treated as part of the CONTEM trials in centres with experience and expertise.

We now have several novel radiation techniques available at our disposal in managing different stages of rectal cancer. This has allowed us to choose a modality that is suitable for a particular patient depending on the stage of disease, age and their choice of treatment, offering a personalised approach.\textsuperscript{11}

**References**