Contact radiotherapy for elderly patients with early low rectal cancers

The National Bowel Cancer Screening Programme hopes to diagnose early bowel cancer. The dilemma is how best to treat it. The standard of care for rectal cancer is surgery, but not all patients are fit or keen to undergo extirpative surgery. A national guideline for the management of screen-detected malignant polyps is urgently needed.

Cancer Research UK (2013) data showed that the number of new patients with rectal cancer diagnosed in 2010 in the UK was 13970, with approximately a quarter of these being either T1 or T2 N0 stage. Owing to the introduction of the National Bowel Cancer Screening Programme in 2009, the proportion diagnosed with early stage disease is expected to increase from 25% to 50% (Tweedle et al, 2007).

The standard of care for rectal cancer is surgery (National Institute for Health and Clinical Excellence, 2011). A national survey showed that abdomino-perineal excision of the rectum was carried out in 27% of patients with early stage disease (Morris et al, 2008). Surgical mortality increases with age and 30-day mortality for patients with bowel cancer above the age of 80 years is 14%, increasing to 25% in patients over 90 years of age (Tekkis et al, 2005; Rutten et al, 2008). Moreover, surgical complications increase with age and medical comorbidities (Rutten et al, 2008). Therefore, it is best to avoid major surgery for early rectal cancer in elderly patients. The alternative treatment option is to offer contact radiotherapy with or without external beam radiotherapy. If there is residual tumour at the end of treatment immediate salvage surgery can be offered without compromising the patient’s chance of cure (Hershman and Sun Myint, 2007).

Background

Contact or Papillon radiotherapy (also known as X-ray brachytherapy) has been in clinical use for the past 80 years; initially in Berlin (Chaoul and Wachsmann, 1953) then in Montpellier (Lamarque and Gros, 1946) followed by Lyon (Papillon, 1974) and Nice (Gérard et al, 2002). It was introduced into the USA in the early 1970s and the initial encouraging results were validated in non-randomized patients (Sischy and Remmington, 1980). Although over 2000 patients with rectal cancer have been treated using the Papillon technique, this is still not regarded as a standard of care for rectal cancer.

The main drawback of this technique is the lack of large randomized trial evidence to prove its efficacy. There are several reasons for this. First, there is no replacement for the ageing Philips machines which were used, the production of which was stopped in the mid 1970s. Second, fewer than a dozen centres around the world offer this facility and each has treated only a small number of patients. Third, advances in endoscopic equipment allowing endoscopic resection and surgical technologies such as transanal endoscopic microsurgery which compete in offering treatment for patients with early rectal cancer.

Management of early malignant rectal polyp

Contact radiotherapy alone (T1N0M0 <3 cm)

This treatment option should be considered for T1 rectal tumours <3 cm in size without any suspicious lymph node metastases or distant spread (Hershman et al, 2003; Sun Myint et al, 2007). Histological proof of malignancy is required and magnetic resonance imaging scanning is mandatory for local staging. It can be difficult to differentiate between a stage T1 and T2 tumour radiologically. Endorectal ultrasound may help to differentiate between T1 and T2 tumours, but is operator dependant. The risk of lymph node spread from T1 rectal tumour is less than 10%.

For adequately staged T1 malignant polyps, treatment can start with contact radiotherapy alone, especially in elderly and medically unfit patients with high anaesthetic risk (Tables 1–2). Patients are instructed to stay on a low residue diet 3–5 days before the procedure. On the day of treatment, a Micolette micro-enema is given before treatment to clear the bowel. The patient is treated in a prone jack knife position and rigid sigmoidoscopy is carried out.

Table 1. Selection criteria for radical contact radiotherapy

| Exophytic malignant mobile rectal cancer <3 cm |
| Rectal cancer confined to bowel wall (T1) |
| Well to moderately differentiated adenocarcinoma |
| No suspicious lymph node spread (N0) |
| No suspicious distant metastases (M0) |

From Sun Myint et al (2007)
to check the tumour size and position. A treatment applicator is inserted using local anaesthetic gel (lidocaine 2% Instilla gel) to treat the tumour with a 5 mm margin and glyceryl trinitrate ointment (Rectogesic) is applied topically to help relax the sphincter muscles. A radiation dose of 30 Gy is given initially to the tumour (clinical target volume) with 5 mm margin (planning target volume). This high radiation dose (biologically equivalent dose is much higher) is applied directly to the tumour and the dose falls rapidly to 50% at 6.5 mm (depending on the applicator size). As very little normal tissue is treated, there are no significant side effects after the first treatment. In responders, the symptomatic relief in terms of the control of bleeding is immediate in 80% of cases (Sun Myint et al, 2007).

The procedure is repeated after 2 weeks when a further radiation dose of 30 Gy is given. Before the third application, if the tumour is still palpable, it is highly unlikely that it will respond solely to contact radiation (Hershman et al, 2003). External beam radiation or preferably chemoradiation is given using either oral capecitabine 825 mg/m² or 5-flourouracil infusion 1 g/m² concurrently with radiotherapy 45 Gy in 25 fractions over 5 weeks. The dose of chemotherapy (625 mg/m²) and radiotherapy can be modified as necessary depending on the patient’s age and performance status. Short course radiotherapy alone can be considered for elderly patients with poor renal function (glomerular filtration rate <50 ml/min). The tumour usually regresses to superficial ulceration or a small residual nodule.

### Table 2. Exclusion criteria

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated adenocarcinoma</td>
</tr>
<tr>
<td>Evidence of lymphovascular invasion</td>
</tr>
<tr>
<td>Deeply infiltrating ulcerative tumours</td>
</tr>
<tr>
<td>Rectal tumour involving more than half the circumference</td>
</tr>
<tr>
<td>Patients not agreeable to long-term follow up</td>
</tr>
</tbody>
</table>

*From Sun Myint et al (2007)*

### Table 3. High risk factors for recurrence

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated adenocarcinoma</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
</tr>
<tr>
<td>Resection margins &lt;1 mm</td>
</tr>
<tr>
<td>Tumour &gt;3 cm</td>
</tr>
<tr>
<td>Depth of invasion &gt;400 um</td>
</tr>
</tbody>
</table>

*From Buch et al (2009)*

**Good responders vs poor responders**

For those who respond well after two fractions (no residual visible or palpable tumour), treatment is continued with contact radiotherapy for a total of four treatments (total tumour dose 110 Gy but biologically equivalent dose is higher) (Figure 1). If there is evidence of small residual tumour (<2 cm) after contact radiotherapy (partial responders), local excision such as transanal endoscopic microsurgery can be considered. However, if the response to contact radiotherapy is poor, with tumour regression of less than 25%, it is important to proceed with radical surgery after 8–10 weeks, as these cases are unlikely to respond to additional radiotherapy (Hershman et al, 2003).

**Local excision for early rectal tumours (T1N0M0 <3 cm)**

Elderly patients with a T1 N0 rectal tumour <3 cm who are fit for surgery can be treated initially by full thickness excision, especially in suspicious polyps with no proof of malignancy even after several attempts of biopsy. If the histology confirms malignancy, with no high risk features (Table 3), and if the resection margins are clear (R0), a watch and wait policy can be adopted (National Institute for Health and Clinical Excellence, 2004, 2011). If the resection margins are involved (<1 mm), if the tumour is staged as pT2 or for those with high risk features, there is a higher risk of local recurrence and distant metastases. Immediate completion surgery should be offered if the
patient is fit and agrees to this option. If the patient refuses surgery, then postoperative chemoradiotherapy with contact radiotherapy should be offered to reduce local recurrence. The dose of contact radiotherapy boost is either 60 Gy in two fractions over 2 weeks (usually) or 45 Gy in three fractions over 4 weeks (pT1 sm3 R0). Long-term results from the Clatterbridge Cancer Centre showed local control in 94% for pT1 tumours (Sun Myint et al, 2012).

Multimodality treatment for more advanced rectal tumours (T1/T2/T3a N0 M0 >3 cm)

In elderly or high surgical risk patients with a more advanced rectal tumour larger than 3 cm in size, the initial treatment should start with chemoradiotherapy (45 Gy in 25 fractions over 5 weeks with capecitabine) or short course external beam radiotherapy alone (25 Gy in five fractions over 5 days) depending on the patient’s general fitness and medical comorbidities. This is to downsize the tumour and in most instances it also downstages the tumour (T1/T2 and some T3a can be downstaged to ypT0 or ypT1).

The response is assessed by endoscopy 2–3 weeks after completion of external beam radiotherapy (8 weeks from the start of treatment). If the residual tumour is less than 2 cm, contact radiotherapy boost can be offered to improve local control. Three fractions of 30 Gy are offered over 4 weeks. Further assessment, with repeat magnetic resonance imaging and computed tomography of the chest, abdomen and pelvis and endoscopy, is carried out at 12 weeks. If there is no residual tumour (complete clinical response) then watch and wait policy can be adopted (Hershman et al, 2003; Sun Myint et al, 2007).

The patient should be made fully aware that this is a non-standard treatment and that salvage surgery will be necessary in the event of recurrence. This usually occurs within 6–12 months in the majority of cases with T1/T2 or T3 rectal tumours. Recurrence can still occur up to 36 months but is rare after 60 months (Hershman and Sun Myint, 2007). If there is suspicion of residual tumour with a small non-healing ulcer or mucosal abnormality, local full thickness excision using preferably transanal endoscopic microsurgery or transanal excision of Parks can be used to establish the histology. In a proportion of patients there will be no residual cancer (ypT0) as the chance of complete pathological response is much higher than complete clinical response (Gerard et al, 2004). If resection margins are clear, then watch and wait policy can be offered. However, if resection margins are involved (<1 mm), then completion surgery should be offered to those who are fit and agree to salvage surgery.

The interpretation of histology after chemoradiotherapy and contact radiotherapy can be difficult even for an experienced pathologist. Therefore, biopsy of the treated area is not advisable if there is no residual abnormality as this can cause persistent residual ulceration or pain. If in doubt, full thickness excision with transanal endoscopic microsurgery should be carried out to clarify the residual tumour status. The restaging magnetic resonance imaging scans following chemoradiation can be difficult to interpret, even by an experienced radiologist, and it is important to repeat magnetic resonance imaging scans every 3 months. In the authors’ experience, if there is a residual tumour it will grow within 6–12 months (Hershman et al, 2003; Hershman and Sun Myint, 2007; Sun Myint et al, 2007). Magnetic resonance imaging abnormalities should be interpreted in conjunction with endoscopy. Digital examination can be useful to assess whether there is residual tumour in patients with low rectal cancer. The patient should be fully aware of the uncertainties and limitations of currently available investigations and accept that salvage surgery may be necessary to resolve the issue. Difficult cases should be discussed at the local colorectal multidisciplinary team meeting and referred to a specialist centre with an experienced multidisciplinary team for an opinion.

Complete response in more advanced rectal cancers (T3/N1/M0)

There is an increasing awareness of complete response following preoperative chemoradiotherapy for advanced rectal cancers. This was first observed by the San Paulo group who reported the concept of ‘wait and watch’ or delayed surgery (Habr-Gama et al, 2004). The chance of local control and cure was not compromised in the cohorts observed and local recurrence could be treated without affecting the long-term survival (Habr-Gama et al, 2006).

A number of international centres are involved in clinical trials to evaluate this further. In the UK, the MERCURY group is conducting a trial on deferral of surgery in complete responders. The North West Colorectal group, which includes Clatterbridge, Preston, North Wales and Christie, is auditing complete responders. There are other reports published on favourable single institution and multicentre pooled data experiences (Maas et al, 2010, 2011). The San Paulo group continues to publish its encouraging mature data which are being observed carefully by surgical communities around the world (Habr-Gama et al, 2010).

Whatever the long-term outcome is, many elderly patients are spared radical surgery without compromising their chance of cure. There is concern about submucosal residual nests of cancer cells which can not be detected on endoscopy or seen on magnetic resonance imaging scans. Small volumes of residual cancer cells can be detected in the operative specimens in patients who had surgery and are not keen to be watched (Smith et al, 2012). This may be an area where a contact radiotherapy boost plays a role as a very high biological dose of radiation is applied directly to the residual tumour with minimal effect on normal surrounding tissues. The high dose of radiation is limited to only a few millimetres of bowel wall (Gerard et al, 2011). The OPERA and CONTEM-5 trials which
evaluate the role of the contact radiotherapy boost may shed some light on this issue.

**Suspicious lymph nodes**

The majority of early staged rectal tumours do not have lymph node spread (<10%). Small lymph nodes (<5 mm) are difficult to evaluate accurately using current investigational tools including magnetic resonance imaging. If there is suspicion of lymph node involvement on endorectal ultrasound or magnetic resonance imaging, the policy of the author’s unit is to offer external beam chemoradiotherapy or radiotherapy to sterilize these lymph nodes. There is now a growing amount of published data on the effectiveness of radiation in sterilizing lymph nodes following preoperative chemoradiation. The probability of residual disease in the lymph node for T3 primary tumours which have been downstaged to ypT0/ypT1 was 2% (Read et al, 2004). However, for advanced unresectable T3–T4 rectal tumour 17% of lymph nodes were found to be involved despite complete response in the primary tumour to ypT0 (Hughes et al, 2006). Therefore, caution is needed before advocating a watch and wait policy that was downstaged after chemoradiotherapy.

A restaging scan 6–8 weeks after treatment is important. If this shows regression of lymph node one can continue to adopt a watch and wait policy. If the restaging scan shows progression (rare in the author’s experience), then immediate salvage surgery is recommended in those patients who are fit. The role of the positron emission tomography/computed tomography scan is still under evaluation and may help in some cases but not in the majority of cases as the equivocal lymph nodes are usually <10 mm (Goldberg et al, 2012).

**Distant metastases**

The chance of distant metastases is less than 5% for early tumours in the authors’ experience (Hershman and Sun Myint, 2007). If distant metastases develop during follow up, surgical resection is offered (if these are operable) for either liver or lung metastases. Contact radiotherapy boost to improve local control can sometimes be offered as a palliative treatment to avoid major surgery in patients presenting with inoperable metastatic disease.

**Follow up**

Close follow up is necessary to detect early recurrence so that salvage surgery can be carried out. Ninety per cent of recurrences occur with the first 2–3 years (Hershman and Sun Myint, 2007).

There are no national or international guidelines on the follow up of patients with complete clinical response. The intensity of follow up needs to be balanced carefully with inconvenience to patients and the cost of investigations involved. The authors recommend that during the period of high risk (usually in the first 2 years) endoscopy should be carried out every 3 months to detect endoluminal recurrences together with a magnetic resonance imaging scan undertaken to detect extraluminal and nodal recurrences. CT scans of the chest, abdomen and pelvis should be carried out at 6, 12, 24 and 36 months. Colonoscopy should be carried out as per national guidelines.

**Side effects**

There is no reported mortality associated with contact radiotherapy. The main side effect is bleeding which occurs in 26% of cases as a result of telangiectasia around the Papillon scar (Figure 2). Bleeding usually settles after 3–12 months.

Patients who are taking anticoagulants or antiplatelet agents can have persistent bleeding and the authors have found that plasma argon coagulation can be useful if the...
bleeding is severe (5%). Rectal stenosis and fistula (rectovaginal) occurred in 1% of cases (usually after transanal endoscopic microsurgery) in the first cohort of patients but none required surgical correction and all responded to conservative treatment. These complications were not observed in the second cohort of patients treated with a new machine (Sun Myint et al, 2013).

Is contact radiotherapy cost effective?
Following extirpative surgery a third of patients end up with a permanent colostomy, including some with temporary stomas that became permanent (National Institute for Health and Clinical Excellence, 2011). The cost of stoma bags varies depending on many factors, but on average, stoma bags cost the NHS £6–8K per patient per annum. At present, a third of patients with early stage rectal cancer in the UK are offered permanent stomas as they are situated in the lower third of rectum (<6cm) (Morris et al, 2008). If these patients can be offered organ-sparing treatments such as contact radiotherapy with or without local excision, over 2000 patients will be spared a stoma. This offers substantial cost savings (in the region of £50–100 million) for the NHS. Health-care policy makers should look into this carefully.

Discussion
The standard of surgical care for low rectal cancer is abdomino-perineal excision with a permanent stoma (National Institute for Health and Clinical Excellence, 2004, 2011). However, mortality and morbidity are high, especially in elderly patients (Tekkis et al, 2005; Rutten et al, 2008). This is becoming an important issue as the ageing population in the UK and other western countries is increasing. The number of people above the age of 85 years will increase from 1.3 million to 3.3 million by 2033 in the UK. In addition, the quality of life for patients who have extirpative surgery and the creation of a stoma is poor (Tekkis et al, 2005; Rutten et al, 2008). Therefore, it is preferable to avoid major surgery and a permanent stoma for small early low rectal cancer in elderly patients. The accepted alternative treatment is local excision using either transanal endoscopic microsurgery or transanal resection using Parks procedure. Both these surgical procedures need general anaesthesia and could take up to 1–2 hours. Some elderly patients or those with severe medical comorbidities (American Society of Anesthesiologists stage 3 or 4) are not fit for general anaesthesia. An alternative option that does not require general anaesthesia is to offer these patients contact radiotherapy with or without external beam radiotherapy. There has not been a large randomized trial to evaluate the role of contact radiotherapy in this setting and this treatment option is not usually offered to patients in most colorectal multidisciplinary teams in the UK. However, tumours are likely to relapse within 6–18 months in the majority of patients who are just offered external beam radiotherapy with or without chemotherapy (Sebag-Montefiore et al, 2005).

Contact radiotherapy in the UK
A team from Clatterbridge visited Lyon to study this technique in 1992 and the first contact radiotherapy facility was set up at Clatterbridge in 1993. Since 2005 regular international annual meetings have been held at Clatterbridge. Ariane (a British company based in Nottingham) became interested in developing and producing a new contact radiotherapy machine and the first prototype machine of its kind was made available for clinical use at Clatterbridge. The first patient was treated using the new machine in October 2009 (Sun Myint et al, 2011).

In total nearly 700 patients have been treated over 20 years at Clatterbridge. Training courses for contact radiotherapy were set up at Clatterbridge to train clinicians from other centres. Over 10 centres from around the world have received training and four centres now offer contact radiotherapy using this new machine. The second facility in the UK was set up at Hull in September 2011 and over 25 patients have since been treated successfully. There are plans for more centres in the UK to set up this facility which will provide treatment locally for elderly patients nearer home.

Plans are also in place to set up an international database for an audit to evaluate the results of patients treated under strict CONTEM protocols which are observational studies (Lindegaard et al, 2007). Several randomized trials such as OPERA and CONTEM-5 are also planned. Until results of these trials are available, the controversy around offering contact radiotherapy to elderly patients with early rectal cancer will continue. In the mean time, it is important for colorectal multidisciplinary teams to recognize the potential for this treatment option so that elderly patients, high anaesthetic risk patients and those who are not keen on having a permanent stoma do not miss the chance of better local control and improve quality of life.

Conclusions
Many elderly patients with early rectal cancer would like to avoid major surgery if possible. Contact radiotherapy should be considered for high anaesthetic risk and elderly patients with low early stage rectal cancer. National guidelines are urgently needed so that colorectal multidisciplinary teams can consider contact radiotherapy as one of the treatment options for suitable patients with early rectal cancer.

The author would like to acknowledge the following for their help: Dr K Whitmarsh, Consultant Clinical Oncologist, Dr B Haylock, Consultant Clinical Oncologist and Clinical Director, Mrs K Perkins, Senior Radiographer, Mr R Clements, Consultant Physicist, Mr A Gately, Senior Radiographer, Mr R Clements, Consultant Physicist, Mr A Gately, Senior Physicist, Dr H Wong, Manager, Clatterbridge Cancer Centre, Beighton, Warrington, Merseyside; Dr AS Dhadda, Consultant Clinical Oncologist, Queen’s Centre for Oncology & Haematology, Castle Hill Hospital, Hull;
KEY POINTS

- There is an increasing ageing population in the UK.
- Morbidity and mortality is high following major surgery in elderly patients, so it is best to avoid major surgery in elderly patients with early rectal cancer.
- Many elderly patients would like to avoid major surgery if there is a choice.
- Contact radiotherapy should be considered for elderly and medically unfit patients with early stage low rectal cancer.
- The majority of early tumours can respond and if there is a residual tumour salvage surgery can be carried out without compromising the patient’s chance of cure.