

The GEC ESTRO Handbook of Brachytherapy

SECOND EDITION

PART II: CLINICAL PRACTICE
Gastrointestinal Tract

25

Rectal Cancer

*Arthur Sun Myint, Chris D Lee
and Jean Pierre Gerard*

Editors

Erik Van Limbergen

Richard Pötter

Peter Hoskin

Dimos Baltas



25 Rectal Cancer

Arthur Sun Myint, Chris D Lee and Jean Pierre Gerard

1. Summary	3	9. Treatment planning	6
2. Introduction	3	10. Dose, Dose rate and Fractionation	10
3. Anatomical Topography	3	11. Post treatment monitoring	10
4. Pathology	4	12. Results	10
5. Work Up	4	13. Adverse side effects	12
6. Indications and Contraindications	5	14. Key messages	13
7. Tumour and Target volume	5	15. References	14
8. Techniques	5		

1. SUMMARY

The concept of rectal cancer management has changed rapidly over the past few years. The standard of care in rectal cancer is still surgery. However, there is increasing interest in non-surgical approaches because of recognition of surgical harm especially in elderly patients, whose number is increasing. In addition, most of the surgical protocols are biased towards locally advanced rectal cancer and are not appropriate for early stage rectal cancer. Early disease is increasingly diagnosed through national bowel cancer screening programmes. For limited size rectal cancer (T1, small T2), brachytherapy alone offers an alternative to radical surgery and leads to excellent results without major morbidity. In advanced rectal cancer, a proportion of patients can achieve complete clinical response after external beam chemoradiotherapy (EBCRT) that can be demonstrated on MRI after neoadjuvant treatment. Colorectal Multi-Disciplinary Tumour boards (MDT) are increasingly advocating a 'watch and wait policy' for these good responders in order to avoid major surgical

resection that involves a permanent stoma and this accords with patient preference. A brachytherapy boost either with contact X-ray brachytherapy (Papillon) or HDR rectal endoluminal brachytherapy can increase the chance of complete clinical response. The prospective OPERA trial will provide more clinical evidence on the role of a brachytherapy boost in advanced rectal cancer after CRT to support non operative management. Most patients prefer not to have surgery if there is a conservative alternative which would lead to a better quality of life compared to major surgery with associated morbidity and a possible stoma. For health care providers there are also important cost savings in non-surgical treatment. A brachytherapy boost following neoadjuvant EBCRT will therefore play an important role in future management of patients with rectal cancer. In this chapter, a systematic outline is provided of the indications for brachytherapy, tumour and target volume determination, techniques of brachytherapy application (contact X-ray, endoluminal, interstitial), monotherapy and combined treatment, treatment planning, dose prescription and results with regard to oncological outcome and morbidity.

2. INTRODUCTION

Rectal brachytherapy is used to deliver an additional dose of radiation after external beam chemoradiotherapy (EBCRT) for advanced rectal cancer. Following EBCRT, a proportion of patients will achieve a complete pathological response which varies from 12-20% depending on the radiation sensitivity of the cancer, (good responder vs. non responder) [1], the initial stage of cancer (T1 or T3), the size of the cancer (<3cm or >3cm) [2] and the time interval from surgical resection (<6weeks or >6weeks) [3]. A rectal brachytherapy boost following CRT can increase the complete pathological response [4, 5]. Complete responders following EBCRT can be watched and surgery delayed until local recurrence [6, 7]. If this approach were adopted worldwide, many elderly patients with early rectal cancer would be spared extirpative surgery which can be reserved for those with residual cancer or with recurrence after achieving complete clinical response (CCR). Rectal brachytherapy, either

with contact X-ray brachytherapy or endocavitary or interstitial brachytherapy will contribute to this novel approach in rectal cancer management. Rectal brachytherapy can also be used as a palliative treatment for locally advanced inoperable disease to control symptoms [8].

3. ANATOMICAL TOPOGRAPHY

The anatomical definition of the rectum is not universally agreed. For the purpose of this chapter, we define the rectum as an area above the ano-rectal ring which is situated 3-4 cm above the anal margin from where the location of a rectal tumour should be measured and not from the dentate line which position can vary and is not always easy to identify using currently available imaging techniques. The rectum can be divided into three parts: - lower third rec-

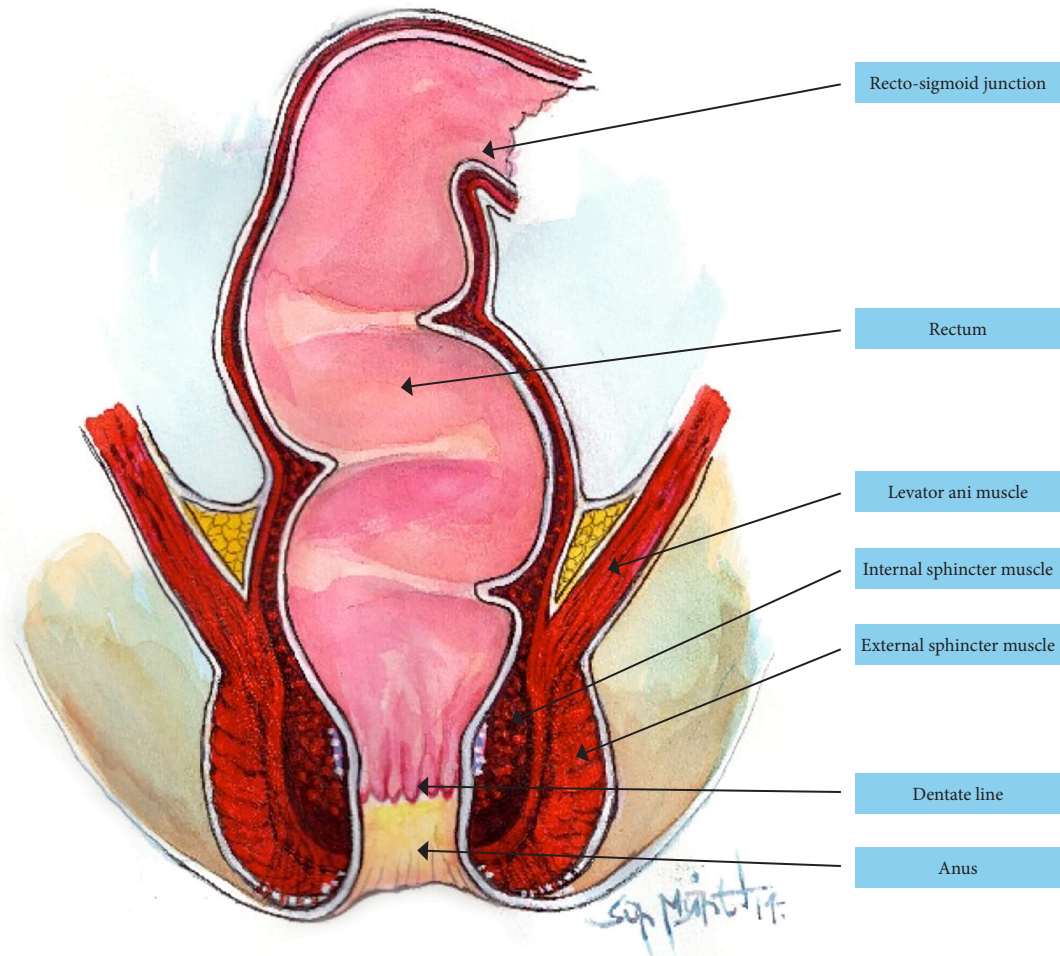


Fig 25.1 : Anatomy of Rectum and anus

tum (4-8 cm); middle third rectum (8-12 cm) and upper third rectum (above 12 cm). The sphincter complex is composed of internal and external portions. The internal sphincter is an extension of the circular smooth muscle of muscularis propria that forms part of the rectal wall. It can be surgically divided without compromising continence which is maintained by the external sphincter contiguous with the puborectalis and levator ani muscles. Long term results from experienced centres using contact X-ray brachytherapy have shown that continence is not affected even when treating very low rectal cancer as the radiation dose that reaches the external sphincter is not high enough to cause muscle damage.

4. PATHOLOGY

Only well to moderately well differentiated adenocarcinomas are suitable for local treatment with brachytherapy or contact RT alone as poorly differentiated cancer has a higher risk of local recurrence and distant spread. Likewise, rectal cancers with lympho-vascular invasion have a higher risk of recurrence and are not suitable for local treatment. The size of the tumour is

important, with those less than 3 cm being suitable for treatment [2]. For larger tumours, external beam chemoradiotherapy (EBCRT) will be necessary to shrink the tumour before rectal brachytherapy. Evidence is now growing from the results of surgical trials that there is down staging of rectal tumours from cT2 or cT3 to ypT0 (12-15%) or ypT1. These patients are now regarded as 'good responders' and they could be offered a boost with brachytherapy to eliminate minimal residual disease to achieve better local control.

5. WORK UP

Endoscopy and digital rectal examination should be carried out before treatment to assess suitability for brachytherapy. The size, location (anterior, posterior or lateral) and height of tumour is recorded carefully together with digital photographs for future evaluation, audit and reference. Biopsy is essential for histological examination to confirm malignancy and to exclude high risk features such as poor differentiation and presence of lympho-vascular invasion (LVI). Radiological staging is important. High resolution MRI of the pelvis is mandatory and should be

repeated at regular intervals following treatment [9]. Contrast enhanced CT scanning to exclude distant metastases is important as this information could change the treatment intent. In case of uncertainty, scans should be repeated at regular intervals to assess this. Endo-rectal ultrasound (EUS) can provide useful information to differentiate between uT1 and uT2 tumours but it is operator dependant. PET/CT scanning is not recommended as part of the initial investigations.

6. INDICATIONS AND CONTRAINDICATIONS

Tumour characteristics such as size (thickness and length), configuration and growth pattern (exophytic or infiltrative) are essential for selecting the appropriate form of brachytherapy whether contact X-ray, endoluminal or interstitial.

Contact X-ray brachytherapy

Selection criteria for contact X-ray brachytherapy are:

- Rectal adenocarcinoma cT1 or cT2 (confined to the bowel wall)
- Well to moderately differentiated cancer
- Mobile exophytic tumour
- Size less than 3 cm in all dimensions
- Location not higher than 12 cm
- Patient must agree to long term follow up

Patients with rectal cancer more than 3 cm in size and stage cT3a or T3b can be offered initial EBCRT or EBRT alone to down size and down stage the tumour. The use of contact X-ray brachytherapy boost can be considered for good responders (>80% regression) with residual exophytic tumours less than 2 cm which penetrate only a few millimetres from the rectal wall.

Exclusion criteria for contact X-ray radiotherapy are:

- Poorly differentiated adenocarcinoma
- Presence of lympho-vascular invasion
- Deeply infiltrative ulcerative fixed cancer
- Tumours involving more than half of the circumference
- Tumours extending into the anal canal below the dentate line

Treatment of multiple cancers is not a contraindication as higher tumours can be treated by surgery and lower rectal cancer treated by x-ray contact radiotherapy. Recurrent tumours are also not a strict contraindication and brachytherapy can be offered if the patient is not medically fit for salvage surgery.

Endoluminal and interstitial brachytherapy

Configuration and bulk of the residual tumour (exophytic or infiltrative) can help to decide which type of brachytherapy boost is suitable following neo adjuvant EBCRT for rectal cancer. HDR endoluminal or interstitial brachytherapy is needed for more infiltrative rectal tumours where the dose can be prescribed at a certain depth. Interstitial rectal brachytherapy should be considered for bulkier, more infiltrative residual rectal cancer. Residual tumours involving more than half of the circumference are suitable for endoluminal brachytherapy as using multiple channels is more appropriate in these cases. Endoluminal brachytherapy can cover the larger residual circumferential tumour bulk by selecting the appropriate number of channels (usually 4-6 channels). In addition, treatment length which is needed to cover the whole

caudo-cranial length of the residual tumour (typically 4-6cm) can be individually selected.

Palliative rectal brachytherapy

Stenotic rectal cancer that does not allow insertion of an endoluminal rectal brachytherapy applicator (e.g. 20 mm diameter) is not suitable for curative brachytherapy. However, a single line source within a small diameter endoluminal applicator as for bronchial or oesophageal brachytherapy (e.g. 2-4 mm) can be used to treat some intraluminal part of the tumor and to allow for tumour reduction and for palliative symptom relief.

7. TUMOUR AND TARGET VOLUME

Determination of the target volume depends on tumour extent (width and thickness), tumour configuration, the time of target determination (at initiation of treatment or after neoadjuvant treatment) and the overall treatment intent.

Limited size tumours

The clinical target volume (CTV) in limited size tumours (<3cm), suitable for x-ray contact brachytherapy (Papillon) or for endoluminal brachytherapy, is the gross tumour itself (GTV) with a margin of 5mm around the tumour (CTV). No further margin is given for the planning target volume (PTV) i.e. CTV=PTV.

Locally advanced tumours

The clinical target volume for rectal brachytherapy in a curative setting for locally advanced disease depends on whether the treatment is given as preoperative brachytherapy alone or as a definitive boost following CRT.

The tumour is intact in preoperative cases and the GTV can be outlined on the CT or MRI scan. The CTV is the GTV plus 5mm margins.

In cases following EBRT or EBCRT, the residual tumour is more difficult to visualise and determination of the tumour position and configuration has to rely on localisation markers, endoscopic findings and post treatment MRI scans. The adaptive CTV is the residual GTV with a margin of 5mm and no further margin is added for PTV (CTV=PTV).

Palliative Treatment Intent

The clinical target volume in palliative treatment may be chosen according to the intent of treatment, e.g. to the intraluminal tumour portion in order to prevent (further) intraluminal tumour growth which would result in progressive stenosis.

8. TECHNIQUES

8.1. Contact X-ray brachytherapy (Papillon)

Preparations before treatment

The treatment can be delivered as an outpatient. Patients are instructed to stay on a low residue diet for 3-5 days and a mini



Fig 25.2. Treatment position for contact x-ray brachytherapy

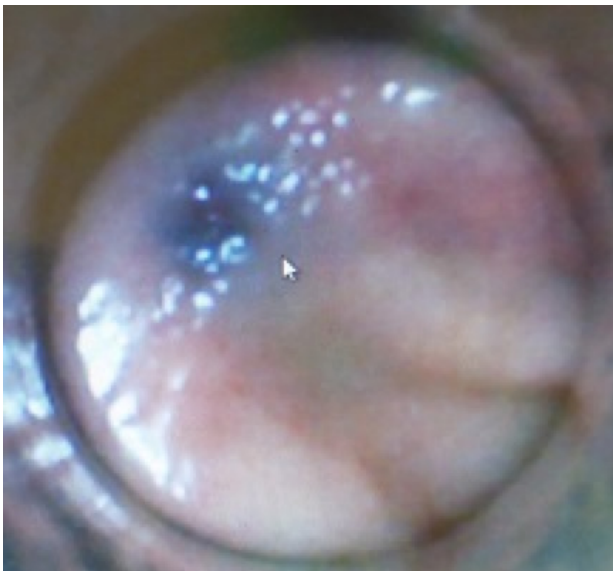


Fig 25.3 Tattoo to identify site of residual cancer where no mucosal abnormality can be detected following chemoradiotherapy (Courtesy of Mr Mike Davies)

rectal enema (micolax) is given 30 minutes before the procedure to clear the bowel.

Treatment Position

The patient is treated on the treatment couch in knee chest position (Fig.25.2). This position helps to open the rectum and makes it easier to identify the tumour. Anterior and laterally situated tumours are easier to treat in this position. However, for low posterior tumours, the lithotomy position may be necessary. Local anaesthetic gel (Lignocaine 2%) is used as topical analgesic in all patients. Glycerine trinitrate (GTN) ointment or a similar preparation can be used to help relax the sphincter muscles. In small number of patients with low pain tolerance, sublingual Fentanyl preparations can be used to control discomfort during the treatment procedure. The disposal rigid sigmoidoscope is first inserted to identify the tumour, assessment of its size and its location. The treatment applicator is then inserted and placed directly to encompass the tumour with a small margin of about 1mm. It is important (when possible) to place the applicator directly perpendicular to the surface of the rectal mucosa where the tumour

is situated. In a small number of cases following neoadjuvant chemoradiotherapy, it may not be possible to identify the site of the residual tumour and a small tattoo may be necessary to help identify the site of the original tumour (Fig. 25.3). However, in the majority of cases a small scar can be seen at the site of the original tumour. There are three sizes of treatment applicators available- 30mm, 25mm and 22mm. A suitable size of applicator size is chosen to cover the scar with a margin of about 5mm.

Dose and acute response

This technique uses a high dose (30 Gy) of low energy (50 kV) x-rays to a small volume (5cm³) every two weeks, applied straight on the tumour under direct vision. The tumour is 'shaved' off layer by layer with each treatment fraction. In responsive tumours, there is no residual cancer at the end of treatment visible on endoscopy (Fig.25.4.a-c), palpable on digital examination or detectable using MRI or CT imaging. This response is sustained when the rectal cancer is cured. The majority of residual tumours will grow back within 6-18 months [10].

Post treatment management

Most patients tolerate the treatment well. A small number of elderly patients (<5%) suffer from postural hypotension and must be positioned appropriately. Rectal perforation or uncontrolled rectal bleeding due to the treatment has not been reported. Patients who develop tenesmus due to radiation proctitis can be treated conservatively with rectal steroid enemas. A small number of patients may develop pain (<5%) and need strong analgesics if the tumour is situated low in the rectum close to the dentate line. The treatment is repeated at two weeks intervals.

8.2 Endoluminal HDR rectal brachytherapy (Ir-192 or Co-60)

The location of the tumour in the rectum is detected by digital examination and endoscopy. Markers are placed below and above the tumour (if possible) to identify the tumour location (Fig. 25.5a). With the patient in the lithotomy position, a rectal applicator, either a multiple channel [4, 5] or a single line (rectal/vaginal) applicator [8] is inserted using local anaesthetic gel and the position is checked using fluoroscopic screening. When the rectal applicator position is satisfactory, it is secured in place using a clamp or corset system. A CT planning scan is carried out in the supine position (Fig 25.5 b). The treatment is carried out after dose calculation and prescribing (Fig 25.5c-g).

8.3 Rectal interstitial implant (Ir-192 or Co-60)

Needles are implanted through the perineum using a template or special Papillon rectal applicator [11, 12] (Fig. 25.6). Treatment is carried out with HDR afterloaders.

9. TREATMENT PLANNING

9.1 Contact X-ray radiotherapy

The prescribed dose of 30 Gy is targeted at the level of the rectal mucosa which corresponds to the base of the exophytic tumour. The dose at the surface of the tumour which protrudes into the treatment applicator is much higher than the prescribed dose.

Fig. 25.4 Rectal Cancer before, during and after contact X-ray brachytherapy (endoscopic findings)

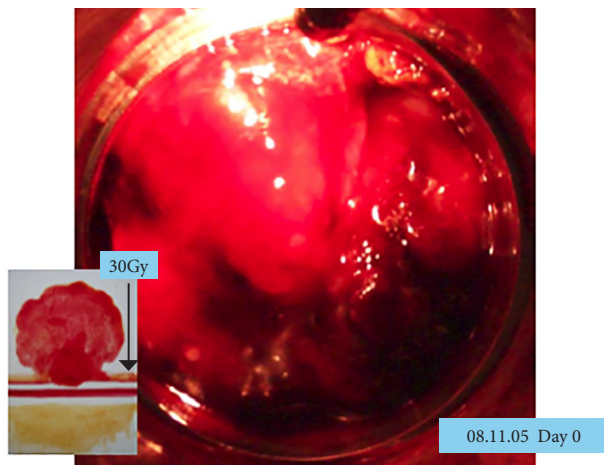


Fig 25.4a Malignant polyp before treatment (day 0)

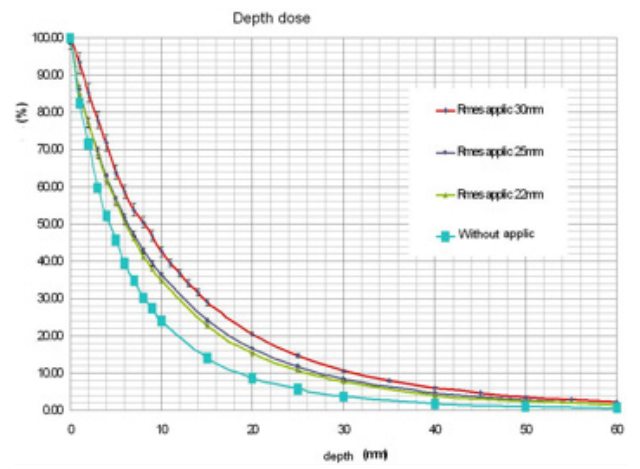


Fig 25.4d: Depth dose curve of contact X-ray brachytherapy for different applicator sizes

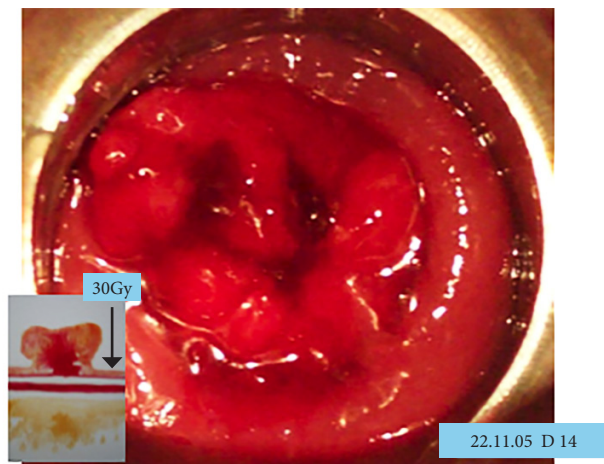


Fig 25.4b Response after one fraction of contact x-ray brachytherapy 30Gy (day14)

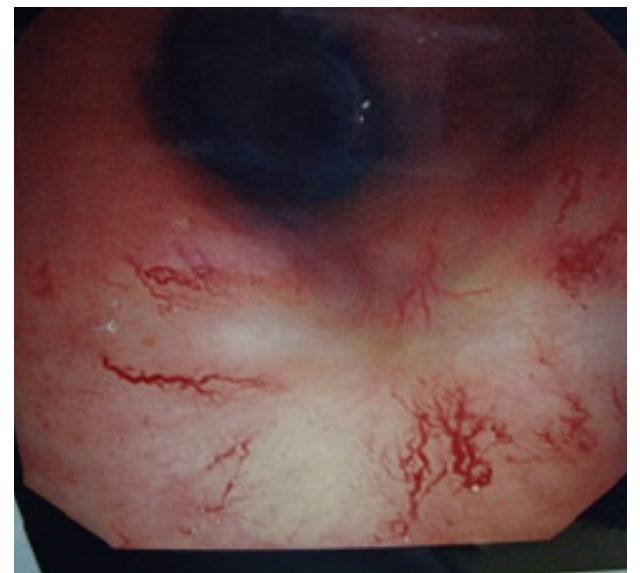


Fig 25.4e Post contact X-ray brachytherapy (Papillon) scar with pale centre and telangiectasia around the scar

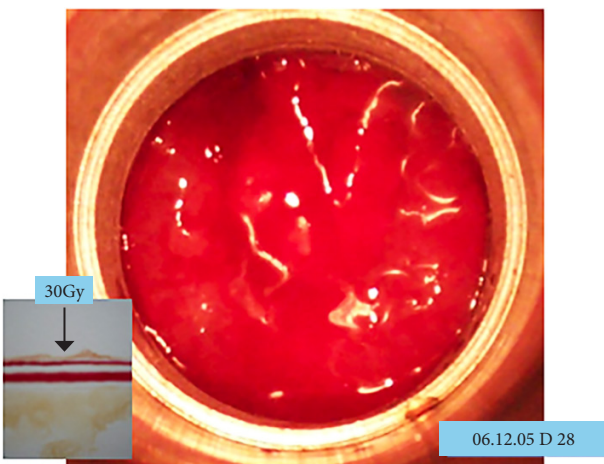


Fig 25.4c Complete clinical response after 2nd fraction 30Gy (day 28)

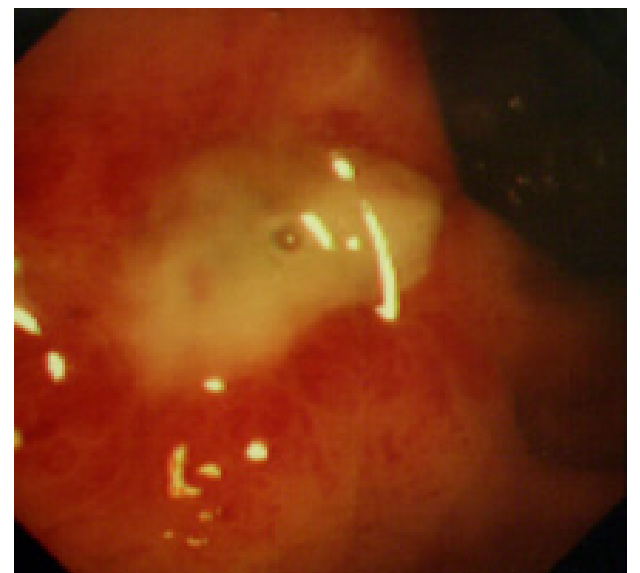


Fig 25.4f Superficial ulcer following brachytherapy which usually heals after 3-6 months.

Fig 25 HDR endoluminal brachytherapy for rectal cancer



Fig 25.5a Radiograph of rectal endoluminal applicator with dummy wires and gold marker seeds indicating tumor borders

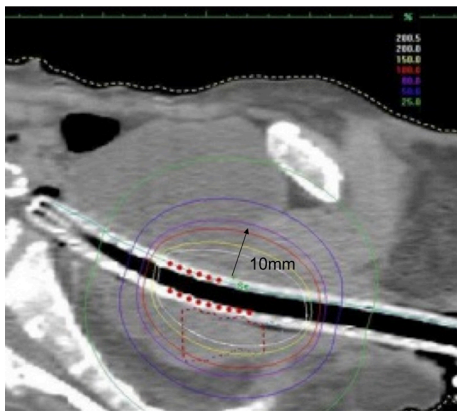


Fig 25.5b Sagittal CT with endoluminal applicator, target volume, dwell positions and isodose lines

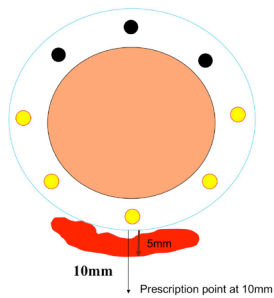


Fig 25.5c Diagram of multi-channel intraluminal rectal brachytherapy with loading positions in posterior part of the applicator for the posterior residual tumour. No loading on the contra lateral side to reduce dose to the non-involved normal rectal mucosa not involved by the tumour. Balloon can also be used to push the normal rectal mucosa away from the loaded positions.

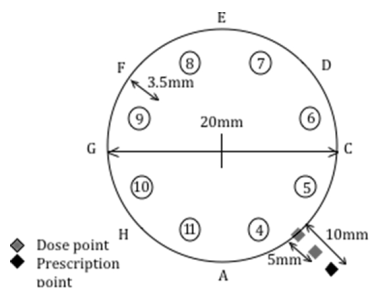


Fig 25.5d Cross section of flexible rectal applicator showing the dimensions, the catheter numbering (4-11) and the calculation points (A-H) midway between each catheter, 10 mm from the applicator surface

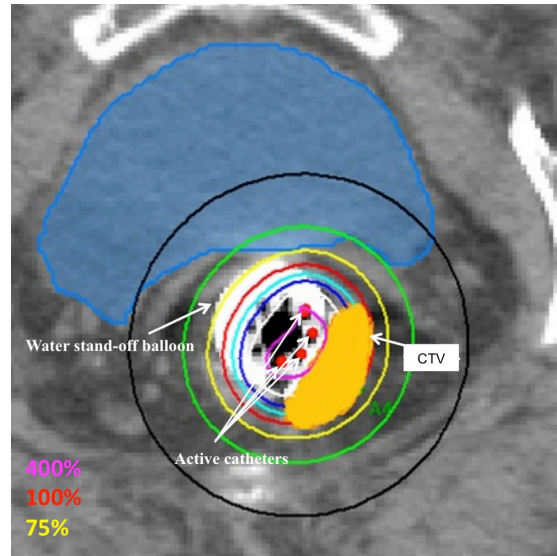


Fig 25.5e CTV (Tumour +5mm) and axial dose distribution with the multi-channel flexible rectal applicator showing the effect of the water stand-off balloon (Courtesy of Dr Te Vuong)

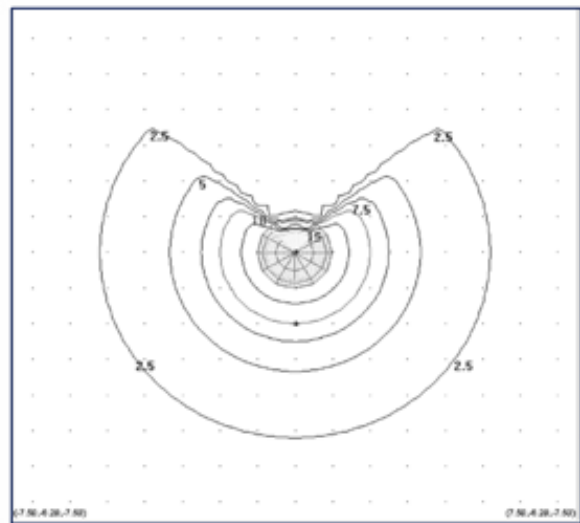


Fig 25.5f Isodose distribution showing effect of quadrant shielding on the dosimetry



Figure 25.5g. Showing rectal HDR endoluminal brachytherapy applicator in treatment position

The treatment is delivered using low energy x-rays (50 kV). For the 30 mm diameter applicator, the dose falls to 60% at 5 mm depth and 38% at 10 mm. For smaller size applicators such as the 22 mm diameter applicator, the corresponding depth dose data at 5 mm and 10 mm are 55% and 34% of the surface dose respectively (Fig. 25.4d). The muscularis propria (MP) is usually situated at 3-5 mm from the surface of the rectal mucosa and tumours infiltrating into the submucosa (T1) will receive more than 85% of the prescribed dose at depth. For T2 tumours (invasion of the MP) the depth dose depends on the depth of infiltration into the rectal wall. If possible, minimum prescribed dose should be also reported at the target depth, in particular for T2 tumours.

9.2 HDR endoluminal brachytherapy

For preoperative HDR rectal brachytherapy the dose is prescribed at the target depth to cover the tumour (GTV) with a margin of 5mm (CTV) (CTV=PTV), provided the prescribed depth is not more than 30 mm. With a prescription at more than 30 mm depth, the dose at the surface will be more than 400%. Such high dose could result in late toxicity for those not fit for surgery or who refuse surgery. In an attempt to reduce the dose to the unaffected normal mucosa, water filled balloons have been used to push the unaffected region away from the radiation source and to reduce toxicity. (Fig 25 5e)

For a boost treatment, the dose is prescribed at 10 mm depth from the surface. However, when the CTV depth becomes more than 10mm due to major residual tumour thickness, the dose may be prescribed to this CTV depth, provided the surface dose at the mucosa does not exceed 400% of the applied dose to reduce toxicity. The maximum of prescribed dose should be also reported at the mucosal surface.

Multi-channel applicator reconstruction and planning

To compute a dose distribution, the applicator must be reconstructed within the planning system. However, the reconstruction technique will depend on the imaging modality employed.

Orthogonal x-rays (Fig 25.5a) Radio-opaque marker wires are inserted into the relevant catheters and orthogonal x-ray images acquired. These images allow the treatment length and any offset from the applicator tip to the treatment region to be determined. From the 8 circumferential channels in the applicator, the most appropriate are chosen depending on the location and extent of the tumour. The applicator geometry can be set up in the planning system and stored for use in the applicator library. To create the treatment plan, the geometric applicator will have to be adjusted for the number of catheters used, treatment length required, the first dwell position accounting for any offset from the applicator tip, and any dwell position weighting. The dose is prescribed to the mean of defined points 10 mm from the applicator surface, equidistant between loaded catheters (Fig. 25.5 c+d). In addition, doses can be reported at additional radial points created during the planning process. This simple 2D treatment planning technique is quick and easy to perform and will produce standard dose distributions. It does not however allow for any significant dose optimisation or dose volume histogram (DVH) analysis. In order to carry out this more complex planning, a full 3D image data set is required from CT or MRI.

CT planning (Fig. 25.5b) Firstly, marker wires are inserted into channels 8, 11, 7 and 4 and true anterior and lateral images ac-



Figure 25.6 Showing interstitial needle implant using anal /rectal jig

quired to check for applicator rotation. When there is zero degrees rotation, the marker wires in channels 8, 11 and 7, 4 are superimposed in the anterior exposure. With the applicator secure in this position, the patient is scanned and a CTV outlined allowing a 1cm margin superiorly and inferiorly to the GTV as defined by pre-inserted marker seeds. Dwell positions are selected appropriately relative to the outlined CTV and the dose is normalised to the mean of applicator points at a distance from the applicator surface, equidistant between loaded catheters, such that the 100% isodose adequately covers the CTV. Computerised optimisation may be necessary to achieve acceptable coverage such that the $V_{100} \geq 90\%$ (100% of the prescribed dose covers at least 90% of the CTV). In addition, by using a combination of marker wire and marker seeds, the distance to dwell position 1 (required for planning and treatment) can be determined. Immediately before each fraction, the applicator rotation is checked using x-ray imaging (as previously explained) and adjusted if necessary. The off-set distance from the applicator tip to the rectal marker seeds is also noted and altered if required. The advantage of the multi-channel applicator is that by selecting the appropriate catheters adjacent to the tumour, the normal tissues will be spared from receiving the maximum surface dose as a result of the inverse square law. This dose can be reduced even further by the application of a water stand-off balloon fitted over the applicator. As the balloon is filled with water, it serves to secure the applicator in position but more importantly, to reduce the dose significantly to the contra lateral tissues (Fig 25.5 e).

9.3 Interstitial HDR brachytherapy

Needles are implanted in single plane using an anal /rectal jig to cover the residual tumour PTV with a margin of 5 mm. Usually 5-6 needles are required depending on the bulk of residual tumour. The length of needles chosen depends on the cranio-caudal length of the residual tumour. A radio-opaque localisation seed is placed at the lower end of the tumour to ensure adequate coverage of tumour within the PTV. Endo-rectal ultrasound (EUS) helps to identify the thickness of the residual tumour (Fig 25.6).

9.4 Palliative brachytherapy

Patients with bulky residual tumours not suitable for endoluminal HDR or interstitial implant are offered palliative brachyther-

apy to control symptoms. These are usually circumferential and fixed tumours and patients are offered radical surgery (Abdomino-Perineal Excision of Rectum-APER). However, those patients who are not fit for such extensive surgery due to multiple co-morbidities or advanced age can be offered palliative brachytherapy. The PTV does not usually cover the whole tumour but the area causing most of the symptoms (e.g. an exophytic area within the tumour causing bleeding).

Single line source applicator reconstruction and planning

For elderly frail patients and for palliative treatments, a single line source applicator can be used. The applicator can be a simple 2 mm diameter plastic tube similar to that used for intraluminal brachytherapy of the bronchus. The treatment length is defined clinically and the dose is prescribed to a point 10 mm from the source train axis midway along the treatment length. As an alternative to the thin plastic single line source applicator, if the lumen allows, a larger diameter applicator such as a rigid plastic applicator of 20 mm diameter, can be used. Planning is relatively simple, similar to the thinner applicator in as much as the dose is prescribed to a point 10 mm from the applicator surface midway along the treatment length producing a cylindrical dose distribution. A variation of this applicator attempts to shield the uninvolved rectal tissues thereby reducing morbidity by employing quadrants of tungsten which can be inserted into the applicator. The axial dose distribution through the centre of the treatment length showing the effect of a single quadrant of shielding can be seen in (Fig 25.5f).

10. DOSE, DOSE RATE AND FRACTIONATION

10.1 Contact x-ray brachytherapy (Papillon)

For radical contact X-ray brachytherapy alone, 3 fractions of 30 Gy are given with one fraction every 2 weeks resulting in a total physical dose of 3 x 30 Gy. If residual tumour is visible or palpable during the last fraction, a 4th fraction of 20 Gy is given resulting in a total of 4 fractions over 6 weeks with 3 x 30 Gy and 1 x 20 Gy.

For contact X-ray radiotherapy as a boost following EBCRT (45 Gy in 25 fractions over 5 weeks or 25 Gy in 5 fractions over 5 days), 3 fractions are applied of 30 Gy each over 4 weeks. The equi-effective dose is 100 Gy (EQD2, alpha/beta = 10Gy) for 1 fraction of contact x-ray brachytherapy of 30 Gy. The total local dose for the shrinking tumor becomes then finally 344 Gy (EQD2) when using EBRT of 45 Gy in 25 fractions or 331 Gy (EQD2) when using 25 Gy in 5 fractions. However, the dose effect may be even higher when assuming a higher RBE for low energy orthovoltage x-rays.

10.2 HDR endoluminal brachytherapy

Pre-operative brachytherapy alone (monotherapy) is given in 4 daily fractions with 6.5 Gy per fraction (target depth dose) resulting in a physical overall dose of 4 x 6.5 Gy. It is given on consecutive days. Surgery is carried out within 6-8 weeks after the end of treatment [4].

When HDR brachytherapy is given as a boost after EBCRT, there is still no internationally agreed dose and fraction schedule (currently under investigation). A dose per fraction of 7-10 Gy at

10mm depth from the surface of the applicator in 3 fractions given at weekly intervals has been used (23).

10.3 interstitial BT dose

The dose for interstitial HDR brachytherapy using an anal jig is 4.5Gy in 3 fractions over 24 hours. This delivers the equivalent dose of 20 Gy (EQD2) as a boost following EBRT.

10.4 Palliative BT dose

Palliative brachytherapy is given using a single line source with cylinder (POVA) postoperative vaginal type applicator or endo-bronchial tube. The dose of 10Gy at 10mm from the surface of the applicator or from the perpendicular midpoint of the line source is prescribed to control symptoms such as bleeding (8).

11. POST TREATMENT MONITORING

Patients should be reviewed at regular intervals during the first two years following treatment, when the likelihood of recurrence is higher. There is no international consensus on frequency of monitoring. However, the monitoring is similar to the watch and wait group where patients are seen every 3 months in the first year, 4 monthly in the second year, 6 monthly in the third year and annually up to 5 years. Late recurrences beyond 5 years are very rare. At each visit, clinical examination, including digital rectal examination, is carried out followed by rigid sigmoidoscopy which alternates with flexible sigmoidoscopy every 3 months. At present, there is no internationally agreed imaging protocol but the suggested protocol follows a scheme similar to that for a watch and wait policy. This includes MRI scans of the pelvis to be carried out every 3 months in the first year, 4 monthly in the second year and 6 monthly in third year. Contrast enhanced CT scanning is carried out at 6 monthly intervals up to 3 years. No radiological imaging is carried out beyond 3 years as the risk of recurrence is low after this time. Any adverse symptoms are recorded and advice is given on how to manage them.

12. RESULTS

12.1 Contact X-ray brachytherapy (Papillon)

Contact X-ray brachytherapy is effective for early stage rectal cancer provided suitable cases are selected carefully. The overall local control rate is between 80-90% depending on the stage of rectal cancer at presentation. The overall survival is between 70-80% which reflects the selection of elderly patients whose survival is limited by their medical co-morbidities and their advancing age.

X-ray contact brachytherapy (Papillon) has been practiced for over 80 years. It was first used in Berlin in the early thirties, and then in Montpellier after the Second World War.

Papillon in Lyon popularised this technique which bears his name and reported a 5 year survival of 74% in 312 patients with T1 rectal cancer treated by contact x-ray brachytherapy alone from

Table 25.1 Overall results of Contact X-ray brachytherapy for early rectal cancer

	COUNTRY	NO	LC	SURVIVAL
PAPILLON [14]	France	312	91%	85%
GERARD [17-20]	France	106	87%	78%
MAINGON [23]	France	15	81%	67%
SISCHY [15]	USA	227	95%	92%
HULL [24]	USA	126	79%	82%
MYERSON [16]	USA	199	80%	86%
MENDENHALL [25]	USA	34	85%	90%
SCHILD [26]	USA	20	89%	76%
SUN MYINT [21-22]	UK	242	89%	75%

1951-1987. There were 9 local recurrences (3%) and only 7.7% of patients died from a cancer related cause [14]. In 1980, Sischy from the Highland Hospital in Rochester (New York) reported a series of patients with limited rectal carcinoma who had been successfully treated by contact radiotherapy. Out of 74 patients treated for cure, only 4 patients (5%) had local failure. Seventy patients who were followed up for at least 18 months were alive and well and free of disease (94%) [15]. Investigators from Washington University at St Louis reported on 199 patients treated from 1980 to 1995. The most important factors for local control (multivariate analysis) were use of external beam radiotherapy ($P < 0.001$), prior removal of macroscopic disease ($P = 0.001$) and tumour mobility on palpation ($P = 0.009$). Endocavitary treatment was very well tolerated. Out of 199 cases, 19 (9.5%) had minor transitory tenesmus or bleeding which was managed conservatively. The only grade 3 or 4 morbidities occurred in those patients who needed salvage surgery for tumour recurrence [16]. Gerard reported on 101 patients with T1/T2 tumours treated with contact radiotherapy between 1977 and 1993. The local failure rate was only 10% with 83% overall survival at 5 years [17]. There was a further report from Lyon of 63 patients with a median age of 72 years and T2 and T3 tumours treated between 1986 and 1998. Twenty six were poor surgical risk patients, 15 refused permanent stoma and 22 who were fit for surgery agreed to radiotherapy to avoid a permanent stoma. Forty patients had a T2 tumour and 23 had a T3 tumour. Patients were offered combined modality treatment with EBRT (39Gy in 13 fractions over 17 days) and a contact radiotherapy boost (80 Gy in 3 fractions over 3 weeks). At a median follow up of 54 months, local control was achieved in 65% and 86% after salvage surgery for residual disease. Primary control rates and 5-year overall survival (for patients <80 years) were 80% and 86% for T2 disease. The respective figures for patients with T3 disease were 61% and 52%. No severe grade 3 toxicity requiring colostomy was observed. Ano-rectal function was good in 92% of patients. Rectal bleeding and bowel urgency were the most common long term side effects. Two prognostic factors were found to be significant: the tumour response on day 21 after two fractions, and T stage of the tumour [18]. Gerard went further to conduct the only randomised trial (Lyon 96-02) to evaluate the role of contact radiotherapy in improving sphincter preservation for T2-T3 distal rectal cancer. Between 1996 -2001, 88 patients were randomised between EBRT (36Gy/13/17 days) and EBRT proceeded by contact (Papillon) boost. Sphincter preservation was achieved in

76% in the experimental group compared to 44% in EBRT alone group. Much higher complete clinical responses (24% vs. 2%) and pCR or near complete sterilization (57% vs. 34%) were observed in the contact boost arm compared with the standard arm [19]. These results were maintained in a recent update after 10 years follow up [20].

Gerard is now proposing the OPERA trial to try to reproduce these results. Organ preservation with local control at 2 years will be the primary end point instead of sphincter preservation. The analysis of the initial first 100 patients treated at Clatterbridge Cancer Centre between 1992 and 2002 with early rectal cancer was similar to reported literature results. At a median follow up of 33 months (range 3-120 months), local recurrence occurred in 10 patients (10%). Six patients had salvage surgery (60%) and one refused surgery although the recurrence was operable. Cancer specific survival was 96% after salvage surgery and overall survival was 77% reflecting the elderly patient population with significant co-morbidity to which they finally succumbed [21]. In the second extended cohort of 220 patients from Clatterbridge, out of 196 patients who achieved a complete remission, 11 (5.5%) developed local recurrence and 7 patients needed delayed salvage surgery. Six were cured (86%). Seven (3.5%) had distant relapse and two (1%) had both local and distant relapse. 24 patients (11%) had persistent disease after combined modality treatment. Twenty one (21/24) had immediate surgery and 19 (90%) were cured. Three patients were not fit for surgery and died of their disease. The overall salvage rate of all recurrences was 30/44 (68%). The overall cure rate after salvage surgery was 202/220 (92%) [22].

12.2 HDR endoluminal rectal brachytherapy

Preoperative brachytherapy alone

Most of the work for the technique of pre-operative endoluminal HDR brachytherapy as monotherapy has been carried out so far by the Montreal group. Several publications from Montreal suggest about 29% pCR following preoperative endoluminal HDR brachytherapy with 24 Gy at depth which covers the PTV in 4 fractions with acceptable toxicity and no increase in post-operative complications [4].

Brachytherapy as boost after chemo-radiotherapy or radiotherapy

This treatment is offered as a fractionated boost in Montreal and Leiden. There is no consensus on dose fractionation for this ap-

Radiation Dose- Response Model (EQD 2)

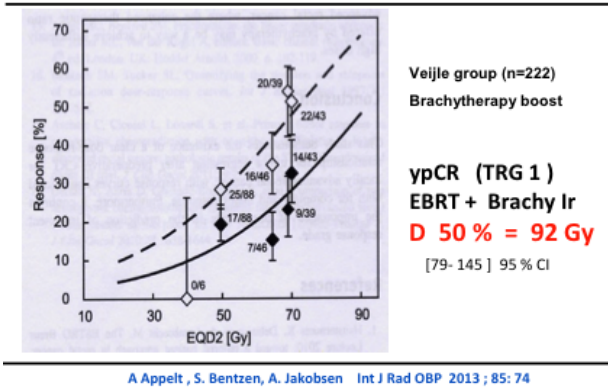


Fig 25.7 Radiation dose response model for rectal cancer [30]

proach. The Montreal group applies 10 Gy per fraction at 10 mm of the applicator surface in three weekly fractions after 50.4 Gy in 28 fractions over 5.5 weeks EBRT. The HEBBERT trial from the Leiden group was a dose searching trial which recommends 7 Gy per fraction in 3 weekly fractions at 10 mm depth from the surface of the applicator after 39 Gy in 13 fractions over 3.5 weeks EBRT [27]. Investigators from Clatterbridge use an HDR brachytherapy boost for bulky infiltrative residual tumours following 45 Gy in 25 fractions over 5 weeks of EBCRT. The dose prescribed was 10 Gy at 10mm from the surface of the applicator, which is similar to the Danish group (see below). They achieved 30% pCR in their cohort of 30 patients [5]. For the elderly and medically unfit group, they used HDR with a dose of 10Gy at 10 mm from the applicator surface followed by contact X-ray brachytherapy [28]. The only randomised trial is from the Danish group who showed no increase in sphincter preservation-their primary end point- in the boost group. However, there was more down staging and higher R0 resection rates in T3 tumours [29]. The criticism of this trial was that the boost dose of 10Gy given in two fractions of each 5 Gy at 10 mm following EBCRT was too low to show a difference. Analysis of the radiation dose response model has shown that a minimum radiation dose of 72 Gy is necessary to achieve major tumour response. Radiation dose escalation to 92Gy is necessary for complete sterilisation of 50% of the tumour. Much higher radiation doses (> 92 Gy) are necessary to sterilise the whole tumour completely (30). Brachytherapy including contact x-ray is the only effective way to escalate the radiation dose significantly to achieve complete sterilisation of rectal cancer without undue toxicity. Doses of this magnitude can not safely be delivered to the rectum by external beam radiotherapy alone, even using modern advanced technologies. New rectal brachytherapy trials using multiple fractions of higher dose are planned.

12.3 Palliative Brachytherapy

Data from Mount Vernon Hospital in a series of 52 patients receiving hypofractionated brachytherapy in one (10Gy) to six fractions (36Gy in 6 fractions) showed that rectal bleeding responded in 75% of patients with complete control in 65% of patients. Pain responded in 83% with complete control of pain in half the patients. Mucous discharge was reduced in about 80 % of patients (8).

13. ADVERSE SIDE EFFECTS

Bleeding is the main side effect which occurs in 26% of cases [13]. This is usually grade 1 or 2 (15%). It may start at 3-6 months and settles after 12 -18 months. This is due to telangiectasia caused by radiotherapy (Fig 25 4e). Bleeding can be troublesome in patients who are on anticoagulants. Grade 3 bleeding is seen in < 5 % and can be treated effectively by argon plasma coagulation (APC). Patients do not need repeated blood transfusions for anaemia related to bleeding from the treatment area. Rectal discomfort, urgency and tenesmus occur in about 10% of cases. Steroid enemas may help. This usually settles after 4-6 weeks. Brachytherapy causes a small superficial ulcer at the site of tumour in most cases which is usually asymptomatic and heals after 3-6 months (Fig 25 4f), unless there is residual tumour. It is important not to biopsy this ulcer as the histology may be difficult to interpret and there may be problems with healing resulting in pain and bleeding.

Rectal tumours which extend into the anal canal are not treated either by contact X-ray radiotherapy or HDR endoluminal rectal brachytherapy. Anal incontinence to liquid stool and air is not common after contact X-ray brachytherapy as the radiation dose received by the anal sphincter muscle is very low.

Fistulas and rectal stenosis occur in <1% and are associated with prior surgical intervention e.g. TEMS (Trans-anal Endoscopic Micro Surgery).

There are no known deaths related to contact X-ray brachytherapy or HDR endoluminal rectal brachytherapy. No rectal perforation or uncontrolled bleeding immediately following treatment has been reported. The results from trials with patient reported outcomes will provide further insight into quality of life after treatment. Knowledge about side effects is at present mainly based on physician reported morbidity.

14. KEY MESSAGES

- Indication for brachytherapy is limited size rectal cancer (T1, small T2) as monotherapy, or limited residual disease after combined radiochemotherapy in advanced cancer (T3a, T3b).
- For limited size tumors, contact therapy can be performed (3x30 Gy \pm 20 Gy) to achieve 80-90% local control without major side effects.
- For advanced disease, radiation dose escalation can be achieved with brachytherapy boost to the residual tumour using contact X-ray brachytherapy giving 90Gy in 3 fractions in addition to external beam radiotherapy of 45Gy in 25 fractions.
- A minimum radiation dose of 72 Gy is necessary to achieve major tumour response. Radiation dose escalation to 92Gy is necessary for complete sterilisation of 50% of the tumour. Much higher radiation doses (> 92 Gy) are necessary to sterilise the whole tumour completely (Fig. 25.7 [30]).
- Brachytherapy including contact X-Rays is the only effective way to escalate radiation dose significantly to achieve complete sterilisation of rectal cancer without undue toxicity. Doses of this magnitude can not safely be delivered to the rectum by external beam radiotherapy alone, even using modern advanced technologies.

15. REFERENCES

- Patel UB, Taylor F, Blomqvist L *et al.* Magnetic Resonance Imaging - Detected Tumour Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience *J Clin Oncol* 2011; 29:3753-3760
- Bach S, Hill J, Monson J *et al.* A predictive model for local recurrence following transanal endoscopic microsurgery for rectal cancer. *Br J Surgery* 2009; 96:280-290
- Francois Y, Nemoz C, Baulieux J *et al.* Influence of this interval between Preoperative radiation therapy and surgery on down staging and the rate of Sphincter saving surgery for rectal cancer: Lyon R90.01 randomised trial. *J Clin Oncol* 1999; 17:2396-2402.
- Vuong T, Devic S, Podgorsak E. High dose rate endorectal brachytherapy as neoadjuvant treatment for patients with resectable rectal cancer. *Clinical Oncology* 2007;19:701-705
- Sun Myint A, Mukhopadhyay T, Ramani V S *et al.* Can increasing the dose of radiation by HDR brachytherapy boost following preoperative chemoradiotherapy for advanced rectal cancer improve surgical outcomes? *Colorectal Disease* 2010; 12:30-36
- Habr-Gama A, Perez R O, Wynn G *et al.* Complete response after neo adjuvant chemoradiation for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum* 2010; 53:1692-1698
- Mass M, Beets-Tan R, Lambregts D M J *et al.* Wait and see policy for clinical complete response after chemoradiation for rectal cancer. *J Clin Oncol* 2011; 29:4633-4640
- Corner B, Bryant L, Chapman C, *et al.* High dose after loading intraluminal brachytherapy for advanced inoperable rectal cancer. *Brachytherapy*. 2010; 9: 66-70
- Brown G, Daniels I, Richardson C *et al.* Techniques and trouble shooting in high spatial resolution thin slice MRI for rectal cancer. *Br J Radiol* 2005; 78:245-251.
- Hershman M J, Sun Myint A. Salvage surgery after inadequate combined local treatment for early rectal cancer. *Clinical Oncology* 2007; 19:720-723
- Papillon J. Present status of radiation therapy in conservative management of rectal cancer. *Radiother Oncol* 1990; 17:275-283
- Gerard J P, Chapet O, Orthalan C *et al.* French experience with contact x-ray endocavitary radiation for early rectal cancer. *Clinical Oncology* 2007; 19:661-673.
- Sun Myint A, Whitmarsh K, Perkins K *et al.* A preliminary report on toxicity of contact radiotherapy in first 100 patients treated by the new RT50 Papillon machine. *Colorectal Disease* 2013; 15: Abst. P081
- Papillon J. Present status of radiation therapy in conservative management of rectal cancer. *Radiother Oncol* 1990; 17:275-283
- Sischy B. The role of Endocavitary irradiation for limited lesions of the rectum. *Int J Colorectal Disease* 1991; 6:91-94
- Myerson R J, Hunt S R. Conservative alternatives to extirpative surgery for rectal cancer. *Clinical Oncology* 2007; 19:682-686.
- Gerard J P, Ayazac L, Coquard R *et al.* Endocavitary irradiation for early rectal carcinoma T1 (T2). A series of 101 patients treated with the Papillon's technique. *Int J Radiation Oncology Bio Phys*.1996; 34(4): 775-783
- Gerard J P, Chapet O, Orthalan C *et al.* French experience with contact x-ray endocavitary radiation for early rectal cancer. *Clinical Oncology* 2007; 19:661-673.
- Gerard J P, Chapet O, Nemoz C *et al.* Improved sphincter preservation in low rectal cancer with high dose radiation. *J Clin Oncol* 2004; 22:2404-2409.
- Orthalan O, Chapet O, Gerard J P *et al.* Correlation in rectal cancer between clinical tumour responses after neoadjuvant radiotherapy and sphincter or organ preservation. *Int J Radiation Oncol Biol Phys* 2012; 83(2):165-171
- Hershman M J, Sun Myint A, Makin C. Multimodality approach in curative local treatment of early rectal carcinomas. *Colorectal Disease* 2003; 5:445-450
- Sun Myint A, Grieve R J, McDonald AC *et al.* Combined modality treatment of early rectal cancer - the UK experience. *Clinical Oncology* 2007; 19:674-681.
- Maingon P, Guerif S, Darsouni R, *et al.* Conservative management of rectal adenocarcinoma by radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;40(5):1077-1085
- Hull TL, Lavery IC, Sacton JP. Endocavitary irradiation; an option in selected patients with rectal cancer. *Dis Colon Rectum* 1994;37:1266e1270
- Mendenhall WM, Rout WR, Vauthey JN *et al.* Conservative treatment of rectal adenocarcinoma with endocavitary irradiation or wide local excision and post operative irradiation *J Clin Oncol*.1997;15(10):3241-3248
- Schild SE, Martenson JA, Gunderson LL. Endocavitary radiotherapy of rectal cancer. *Int J Radiat Oncol Biol Phys* 1996;34:677e682.
- Marijnen CA. External beam radiotherapy and high dose rate brachytherapy for medically unfit and elderly patients. *Clin Oncol* 2007;19(9):706-710
- Sun Myint A, Lee C D, Sneek A, *et al.* High dose rate brachytherapy as a boost after preoperative chemoradiotherapy for more advanced rectal tumours: the Clatterbridge experience. *Clin Oncol* 2007;19(9):711-7119
- Jakobsen A K M, Pløen J, Vuong T *et al.* The dose effect relationship in pre-operative chemoradiotherapy of locally advanced rectal cancer: A randomised trial comparing two radiation doses. *Int J Radiation Oncol Biol Physics* 2012; 84(4): 949-954
- Appelt AL, Ploen J, Vogelius IV *et al.* Radiation dose response model for locally advanced rectal cancer after preoperative chemoradiotherapy. *Int J Radiat Oncol Biol Phys*.2013;85(1):74-80.

ACKNOWLEDGEMENTS

The authors of this chapter are much indebted to the authors of the original version of the chapter on Anorectal Cancer in the first edition of the GEC-ESTRO Handbook on Brachytherapy Jean Jacques Mazon and Erik Van Limbergen. Furthermore, the content is based on the Papillon teaching course whose teachers should also be acknowledged: Mr Mike Hershman, Prof Geerard Beets, Prof Paul O'Toole, Dr Karen Whitmarsh, Dr Nick Day, Dr Tim Andrews, Dr Aman Dahdda, Kate Perkins, Alan Gateley, Richard Clements, Mark Davies together with past and present members of the GEC ESTRO rectal working group and members of ICONE (International Contact Radiotherapy Network) group.

AUTHORS

Arthur Sun Myint, F.R.C.P; F.R.C.R.
Lead Clinician (Papillon)
Clatterbridge Cancer Centre.
Hon Professor, University of Liverpool
Liverpool, UK

Chris D Lee, BSc (Hons); MSc.
Consultant Physicist, Head of Brachytherapy Services
Clatterbridge Cancer Centre, Bebington
Wirral, UK

Jean Pierre Gerard, M.D. Emeritus Professor
University of Nice
Consultant Oncologist, Centre Antoine-Lacassagne
Nice, France