7 Radiotherapy: principles and applications

Introduction

The therapeutic use of radiation in gynaecological cancer quickly followed the discovery of X-rays by Roentgen in 1895 and radium by the Curies in 1898. The aim of radiotherapy is to destroy the cancer if possible without damaging the surrounding normal tissues. The application of a cancericidal dose of radiation to the cancer must be balanced against the inevitable collateral damage caused to local normal organs at risk. Radiotherapy treatment can involve a combination of external beam radiotherapy and brachytherapy. External radiotherapy (teletherapy) employs the use of a high-energy photon (X-ray) beam generated from a linear accelerator. Brachytherapy (Greek brachy, short) involves the use of sealed radiotherapy sources placed close to the treated tissue. The sources may be placed in the natural cavities of the vagina or uterus (intracavitary treatment) or needles or tubes inserted into the tissues (interstitial brachytherapy). The two modalities of external beam radiotherapy and brachytherapy can be combined or used individually.

Radiobiology

Radiotherapy uses the damaging effects of ionising radiation on cellular DNA. X-rays and, less commonly, gamma-rays are the commonly used forms of ionising radiation. The ‘four Rs’ form the basis of radiobiology: repair, repopulation, reoxygenation and redistribution.1

Cancer cells and normal tissue cells vary in their ability to repair the damage caused by radiation. This difference can be exploited by dividing up (fractionating) the dose of radiotherapy to increase the lethal damage to tumour cells, while allowing normal tissues to repair.

During radiotherapy, viable cells will continue to divide. This is the process of repopulation. A course of radiotherapy must kill not only the original tumour cells but also those formed by repopulation during the treatment period.

Well-oxygenated cells are more sensitive to radiation-induced damage...
than hypoxic cells. Reoxygenation is the process whereby relatively hypoxic areas acquire the perfusion left by the more radiosensitive, well-oxygenated cells that have been killed by previous fractions of radiotherapy.

Cells vary in their response to the effects of radiotherapy throughout the cell cycle. Cells in the G1, early S and G2/M phases are highly sensitive, whereas cells in the late S phase are relatively resistant. Fractionation of the radiotherapy exploits this redistribution of cells through the stages of the cell cycle.

**Planning**

Radiotherapy planning involves three-dimensional localisation of the treatment volume and assessment of the surrounding normal tissues. The patient has a CT planning scan (see chapter 4). The clinician draws the target volumes and organs at risk on a planning computer. The planning process outlines the tissues to be treated. The target volume is the demonstrable cancer and any tissues at risk of containing cancer. The principal organs at risk for most gynaecological cancers are the bladder and rectum. A three-dimensional model of the target volume and organs at risk is displayed by the planning department. From that model, a treatment plan showing an isodose distribution is developed, using multiple radiation fields and shielding of normal tissue by multileaf collimators or lead blocks. Inevitably, the bowel and bladder will also receive some radiation but it is the ‘art’ of radiotherapy to plan the beams so that the tumour receives a cancericidal dose while the normal tissue doses remain within tolerance. Tattoos are placed on the patient to aid accurate positioning for each fraction of radiotherapy.

**Implementation of brachytherapy**

Brachytherapy has the advantage of delivering a high dose in the proximity of the sources while limiting the dose to normal tissues. Various intracavity systems have been designed. The ‘live’ systems as originally developed in Paris, Stockholm, Manchester and Sheffield have now been replaced in most of the world by afterloading equipment. Live brachytherapy exposes the operating doctor, the theatre staff and the ward nurses to the risks of radiation throughout the period in which the patient is being treated.

Afterloading systems are mechanical devices that load the actual radioactive sources into the patient remotely once she is on the ward in a protected room. The operating doctor merely inserts non-radioactive tubes in the correct arrangement and the afterloading apparatus is connected to these tubes later. This system protects the staff at the time of insertion and
on the ward. It also allows more time for the radiotherapist to adjust the insertion to ensure the best arrangement to treat the patient and for more flexibility in the arrangement of sources. The most common mechanical afterloading system is the Selectron. The high dose rate Selectron allows the dose to be delivered in minutes and thus on an outpatient basis.

**IMPORTANCE OF RECTAL AND BLADDER DOSES**

The limiting tissues for gynaecological brachytherapy are the rectum and bladder. The tolerances for these tissues were empirically derived. The dose rate to the rectum is reduced by the mechanical spacing imposed by the applicators themselves, any packing inserted by the operating doctor and any inbuilt shielding.

**DOSE PRESCRIPTION FOR RADIOTHERAPY IN CARCINOMA OF THE CERVIX**

The doses of radiotherapy employed in treating carcinoma of the cervix depend particularly on the intracavitary technique and equipment used. The doses are prescribed at conventional Manchester Points A and B. Point A is defined as 2 cm lateral to the midline and 2 cm above the lateral vaginal fornix. Point B is 3 cm lateral to Point A. With combined external and intracavity brachytherapy most clinicians would aim for a combined total dose of 70–80 Gy at Point A and 50–60 Gy to Point B. The balance of the contribution of external and internal radiotherapy used to achieve these doses depends on the individual configuration of the patient’s cancer, and the particular technique and equipment favoured by the clinicians.

The design of radiotherapy for carcinoma of the cervix depends on the extent of the cancer. In general higher stage cancers are given more of the dose from external beam and less from the brachytherapy. Apart from very early cancers it is usual to give the external beam radiotherapy first. This allows the cancer to shrink so that the anatomical arrangement of the brachytherapy improves.

**Adverse effects of radiotherapy**

The radiation tolerance of normal tissues is related to the acute or chronic radiation reactions that occur in them. The acceptable tolerances determine the way in which radiotherapy is planned. Tolerance is a relative term in that we will accept a greater degree of damage to normal tissues if the aim is radical rather than palliative.

The acute reaction encompasses changes that come on fairly quickly, either just after the radiation or within a few weeks of conventionally
fractionated radiation and resolve within a few months of completing treatment. Nausea, diarrhoea, proctitis, vaginitis and redness or flaking of the skin are all manifestations of the acute radiation reaction. Acute reactions usually settle spontaneously and require supportive symptomatic treatment only, although severe acute reactions can cause ulceration, obstruction, and bleeding. Acute bowel reactions are very common during pelvic radiotherapy. At least 70% of patients have diarrhoea, frequent bowel movements, or colic. The presence of an acute radiation reaction does not necessarily predict that a chronic reaction will occur. The mechanism causing these reactions is different but both reactions relate to the dose received by the tissues.

The chronic radiation reaction may take months or years to develop and includes bowel stricture, bladder stricture, fibrosis and adhesions and various fistulae. The chronic bowel morbidity usually appears within 2 years and the urinary morbidity within 4 years, although both can appear many years later.

**Clinical applications of radiotherapy**

**CERVICAL CANCER**

The treatment of cancer of the cervix is very varied between countries, cancer centres and even clinicians. In some situations, particularly for early stage disease, surgery and radiotherapy may be equally effective. The aim is to provide the highest cure rate combined with the lowest associated morbidity (Table 7.1).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>Wertheim’s hysterectomy</td>
<td>The results of surgery and radiotherapy are the same but the morbidity is different</td>
</tr>
<tr>
<td></td>
<td>Radical chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>IIA:</td>
<td>Small volume: Either radical surgery or radiotherapy is appropriate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bulky: Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>IIB–IIIB</td>
<td>Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>Exenterative surgery or chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>Palliative therapy</td>
<td>Palliative radiotherapy or chemotherapy</td>
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Radiotherapy is the treatment of choice for bulky stage IIA to stage IVA disease. Following surgery with lymph node involvement, high-grade disease or close or involved excision margins, postoperative adjuvant radiotherapy may be offered. Cisplatin chemotherapy is given concurrently with radiotherapy. There is also a role for radiotherapy (and chemoradiotherapy) in patients who develop pelvic recurrence after definitive surgery.

ENDOMETRIAL CANCER

Primary radiotherapy may be used for patients who are unfit for surgery. Although inferior to surgery, it has a 60% 5-year survival for stage I disease. Adjuvant postoperative radiotherapy may be given, with either external beam radiotherapy, vaginal vault brachytherapy or both. Adjuvant radiotherapy is offered to patients with poor prognostic indicators, although there is no international consensus for the indications for adjuvant treatment. Local recurrence was reduced but there was no survival benefit in the UK ASTEC trial or the Canadian Clinical Trials Group EN.5 trial. The PORTEC studies showed a reduction in local recurrence for high-intermediate risk patients from 20% to 5%.

Conventionally, patients are divided into three risk groups for recurrence. The addition of adjuvant therapy is based on those risk categories (Table 7.2).

Most endometrial cancers are well-differentiated endometrioid adenocarcinomas. 15% of endometrial cancers are papillary serous or clear-cell type and considered grade 3. These cancers behave more like ovarian carcinomas than endometrioid endometrial cancers but the value of both adjuvant radiotherapy and chemotherapy in these cancers is uncertain and are best managed in a clinical trial. This subject is explored further in Chapter 10.

| Table 7.2 Adjuvant radiotherapy for endometrial cancer |
|----------------------------------------|----------------|
| Risk group   | Grade | Stage                      | Adjuvant radiotherapy               |
| High         | 3     | IC                         | PORTEC3 trial                       |
| Any grade    |       | ≥ IIA                      | Pelvic radiotherapy                 |
|              |       | Lymphovascular space or    | Vaginal brachytherapy               |
|              |       | lower segment involvement  | Possibly chemotherapy               |
| Intermediate | 1–2   | IA–B                       | Vaginal brachytherapy               |
| 3            |       |                            | Possibly pelvic radiotherapy        |
| Low          | 1–2   |                            | No further treatment                |
VULVAL CANCER
Early stage vulval cancer is treated surgically. Radiotherapy (or chemoradiotherapy) is offered for advanced disease or for those unfit for surgery. Adjuvant postoperative radiotherapy is used for close or positive margins, large deeply invasive lesions with lymphovascular space invasion and in patients with positive inguinal lymph nodes or extracapsular spread from one node. Preoperative chemoradiotherapy for locally advanced carcinoma of the vulva does improve operability but adverse effects are severe. For further details on the role of radiotherapy in vulval cancer management, see Chapter 12.

VAGINAL CANCER
Vaginal cancer is a rare cancer and the evidence base for treatment is thin. Small lesions confined to the vaginal mucosa may be treated with vaginal brachytherapy alone. Chemoradiation is offered for locally advanced vaginal cancer by analogy with carcinoma of the cervix.

OVARIAN CANCER
Radiotherapy was formerly used in the treatment of ovarian cancer. With the onset of effective chemotherapy radiotherapy is only offered palliatively.

RADIOTHERAPY FOR SYMPTOM CONTROL IN A PALLIATIVE CONTEXT
Radiotherapy is widely used in the management of pain from bone metastases. Short courses of radiotherapy may stop patients bleeding from inoperable tumour masses in the vaginal vault. For further details of palliation, see Chapter 14.
KEY POINTS

- Four parameters form the basis of radiobiology: repair, reoxygenation, repopulation and redistribution.
- Complications may arise early, owing to acute toxicity or late, from radiotherapy damage.
- Equal cure rates apply for radiotherapy and surgery in early-stage cervical cancer.
- There is a survival advantage for chemoradiation over radiotherapy alone in cervical cancer.
- There is no increase in survival in endometrial cancer through adjuvant radiotherapy but there is a decrease in local recurrence.
- Radiotherapy is widely used in vulval cancer as adjuvant treatment.
- Radiotherapy is primary treatment in vulval cancer if the patient is unfit for surgery or to ‘shrink’ tumour preoperatively.

References
