Radiotherapy is an important treatment modality for 40–50% of children with cancer. There is concern about late effects, particularly the neuropsychological effects of CNS irradiation, and orthopaedic effects. It is important to administer the highest standard of radiotherapy, incorporating departmental quality assurance. Meticulous planning is essential to achieve local tumour control with the minimum of irradiation to normal tissues in order to minimise late effects. Current developments include better definition of tumour extent with MR scanning, and the use of 3D planning and conformal techniques to precisely match the radiotherapy target volume to the tumour. For some CNS tumours the role of stereotactically directed radiotherapy is being explored. Interactions with chemotherapy are important to improve the therapeutic ratio, however increased normal tissue toxicity can be problematic. Radiotherapy for children should be undertaken only in departments linked to specialised paediatric oncology centres.

Radiotherapy is an important modality in the treatment of cancer in children. In 1988, Donaldson reviewing the role of radiotherapy in modern paediatric oncology stated: 'an estimated 70–80% of children with cancer today will need and receive radiotherapy at some time in their course of treatment'. In the last decade, chemotherapy regimens have become more intensive. There is also concern about the late effects of radiotherapy, particularly the neuropsychological effects of irradiation of the CNS, and orthopaedic effects. Consequently, the proportion of children with cancer receiving radiotherapy has fallen to approximately 40–50%. It is incumbent on paediatric radiation oncologists to provide the highest possible standard of radiotherapy. Meticulous planning is essential in order to achieve local tumour control with the minimum of irradiation to normal tissues and minimise late effects. National or international radiotherapy protocols should be used. It is extremely important that the radiotherapy of children should be undertaken only in radiotherapy centres linked to specialised cancer treatment centres. In the UK these form the network of 22 United Kingdom Children’s Cancer Study Group (UKCCSG) paediatric oncology centres.
Production of therapeutic radiation

**Photons**

X-rays form part of the electromagnetic spectrum of photon radiation. High energy X-rays are produced by a linear accelerator. Beam size is determined by collimators, and the shape can be defined further by shaped lead blocks. Usually at least two fields (parallel opposed pair) or multiple intersecting fields are employed, allowing delivery of a high dose to deep tissues. An alternative source of radiation for external beam radiotherapy are gamma rays produced from radioactive decay of $^{60}\text{Co}$.

**Electrons**

Electrons are produced by a linear accelerator. Because of their defined track length within tissue they can be used for the irradiation of superficial tumour volumes, with relative sparing of deeper tissues.

**Neutrons**

Neutrons are produced by a cyclotron and have the potential advantage of being less dependant on the presence of oxygenation within the tumour. They probably have a role in the treatment of salivary tumours and some sarcomas, but they have no routine role in the treatment of children.

**Protons**

Protons which are produced by a high energy cyclotron have the advantage of depositing their energy within the Bragg peak, a short track length at a depth within tissue. These may be valuable for the treatment of small tumours such as ocular, parasellar or skull base tumours where a high radiation dose has to be delivered to a small volume, with sparing of surrounding tissue.

**Brachytherapy**

Gamma rays produced by radioactive decay of radioactive sources such as $^{192}\text{Ir}$ can be used for brachytherapy. This can be achieved by implantation into the irradiated tissue, or within a cavity. Brachytherapy has an established role in the treatment of localised retinoblastoma and for the local control of rhabdomyosarcoma, particularly vaginal, but other sites such as head and neck sites or bladder/prostate may be suitable. Some CNS tumours may be suitable for brachytherapy by stereotactic implantation of radioactive sources.
Interaction of X-rays with tissue

High energy X-rays interact with tissue giving rise to secondary electrons which cause ionisation within the irradiated tissue. The effects are largely indirect as a result of the ionisation of water with the production of free radicals which cause DNA damage. The cell killing effects as well as the mutagenic and carcinogenic effects of radiation result from DNA damage.

With the exception of mature lymphocytes, radiation does not cause immediate cell death. Cells die when they attempt subsequent cell division. The radioresponsiveness of a tissue or tumour is related to cellular kinetics. Tissues with a fast cell turnover, e.g. marrow, will exhibit a more rapid depletion of cells than a tissue with a slower turnover, e.g. vascular endothelium.

Radiotherapy is usually delivered in fractions, given daily on Mondays to Fridays for up to 6–7 weeks. Between fractions, repair of sub-lethal damage (SLD) takes place. This is important for normal tissue tolerance. SLD is repaired with a half life of 1–2 h, and for practical purposes, a minimum of 4 h (and longer when CNS is in the volume) should intervene between fractions.

The international system (SI) unit of measurement of radiation dose, the Gray (Gy) is the equivalent of absorbed energy of 1 joule per kg of tissue.

Time and dose factors

The overall treatment time, total radiation dose and the dose per fraction are related by the linear-quadratic formula\(^{10,11}\):

\[
\text{BED} = \alpha n d + \beta n d^2
\]

where BED is the biologically effective dose, \(n\) the number of fractions, \(d\) the dose per fraction, and \(\alpha\) and \(\beta\) are the coefficients of the effect of dose. This is based on a model of the effect of radiation effect on DNA, and is supported by in vitro and in vivo data. The ratio \(\alpha/\beta\) is different for different tissues. Tissues with a high \(\alpha/\beta\) ratio, typically 10, include the so-called early reacting tissues, such as bone marrow and tumour. Late reacting tissues have a low \(\alpha/\beta\) ratio (1–3) and include lung and CNS. A small dose per fraction will preferentially reduce the late effects on late reacting tissues, particularly the CNS. This provides the rationale for attempts to improve the therapeutic ratio by radiation regimens involving a reduced dose per fraction, e.g. hyperfractionation.
**Definition of target volume for radiotherapy planning**

For the definition of the target volume for radiotherapy planning it is recommended that the recommendations of the current International Commission for Radiation Units (ICRU) ICRU-50 report\(^\text{12}\) are employed. The target volumes are defined as follows:

1. The *gross tumour volume* (GTV) is the gross palpable or visible/demonstrable extent of the tumour.
2. The *clinical target volume* (CTV) is the tissue volume that contains the GTV and/or subclinical tumour. This volume has to be treated adequately in order to achieve local tumour control.
3. The *planning target volume* (PTV) is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effects of all the possible geometrical variations, in order to ensure that the prescribed dose is actually delivered to the whole of the CTV.
4. The *irradiated volume* is the volume that receives a dose that is considered important for normal tissue tolerance.

**Tumour localisation for radiotherapy planning**

The GTV and CTV are determined by one or a combination of the following means.

**Clinical**

This is appropriate in only very limited situations, such as when a palpable tumour is treated with palliative radiotherapy.

**Simulator localisation**

This is the most frequently employed method of tumour localisation. The simulator is a diagnostic X-ray set with the same geometric characteristics as the linear accelerator. The simulator can be used not only to localise tumour, but also to produce a permanent radiological record of treatment planning.
Computed tomography (CT) planning

The tumour is localised on a CT scan, and the target volume defined in relation to the CT tumour image. Definition of the tumour volume on each CT slice can be used to plan a volume to accurately conform to the tumour dimensions (conformal planning).

3D planning

The tumour and surrounding normal structures are imaged in a three dimensional reconstruction. This allows a better definition of the tumour and normal tissues including critical organs. This technique can be combined with treatment using conformal non-coplanar beams. In this way the target volume can be more precisely shaped to the tumour dimensions, giving the potential for reduced irradiation of normal tissues and sparing of late effects.

Immobilisation

Immobilisation during a radiotherapy fraction is important. For radiotherapy to the trunk confirmation of positioning using a laser light system is usually employed. For treatment of tumours of the head and neck, brain, or limb, the manufacture of a perspex shell is essential.

Sedation/anaesthesia

Because of the importance of immobilisation, young children, particularly those under the age of 3 or 4 years, frequently find it very difficult to lie still. The assistance of an experienced play therapist can be very helpful in preparing the child for radiotherapy, particularly when a perspex head shell is required. Sedation sufficient to ensure immobilisation is difficult to achieve without it persisting for several hours. Short acting general anaesthesia such as Diprivan® (propofol) is sometimes essential. The daily fasting for this results in surprisingly little disruption to nutrition.
Radiotherapy quality assurance (QA)

Radiotherapy QA plays a key role in the delivery of the highest quality radiotherapy.

Departmental QA

During the planning process, the positions of all field are checked using a simulator, and X-rays taken of all fields. On-treatment verification films using the linear accelerator are taken to provide a further check of field accuracy. Facilities are now available for providing digital portal images of the radiation field in real time during a fraction of radiotherapy.

QA in multicentre studies

There is evidence that accuracy of delivery of radiotherapy contributes to improved tumour control, particularly when complex techniques such as craniospinal radiotherapy are employed\textsuperscript{13}. In many of the North American multicentre studies, radiotherapy quality, including beam data, dose prescription, planning and verification films are reviewed in the Quality Assurance Review Centre (QARC)\textsuperscript{14}. In most European multicentre studies, QA is less well organised. Ideally, review of planning films should be sufficiently fast to provide rapid feedback in order to modify the treatment plan if necessary. This is logistically difficult but has been achieved in the German multicentre Ewing’s sarcoma studies.

Overview of radiotherapy in the treatment of cancer in children

Radiotherapy is a very effective cytotoxic agent with high local control rates for many paediatric tumours. The role of radiotherapy is summarised in Table 1.

Normal tissue effects

These are classified as acute when they occur during the course of radiotherapy, subacute when they occur within 6 months and late when they occur more than 6 months later.
Table 1  Summary of the current role of radiotherapy in the treatment of cancer in children

<table>
<thead>
<tr>
<th>Tumours treated by radiotherapy</th>
<th>Dose required for local control (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy alone for local control of primary</td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>40-50</td>
</tr>
<tr>
<td>Stage IA Hodgkin’s disease</td>
<td>35</td>
</tr>
<tr>
<td>Low grade glioma</td>
<td>54</td>
</tr>
<tr>
<td>Intracranial germinoma</td>
<td>45</td>
</tr>
<tr>
<td>Eosinophilic granuloma</td>
<td>5-10</td>
</tr>
<tr>
<td>Postoperative radiotherapy for subclinical disease</td>
<td></td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>45</td>
</tr>
<tr>
<td>Stage II Wilms’ tumour</td>
<td>20</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>45</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>55</td>
</tr>
<tr>
<td>Stage III neuroblastoma</td>
<td>24-36</td>
</tr>
<tr>
<td>Radiotherapy for ‘sanctuary sites’</td>
<td></td>
</tr>
<tr>
<td>CNS prophylaxis for ALL</td>
<td>24</td>
</tr>
<tr>
<td>Total body irradiation</td>
<td></td>
</tr>
<tr>
<td>Poor prognosis ALL</td>
<td>14.4 (given in 8 fractions twice daily)</td>
</tr>
<tr>
<td>AML in first remission</td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td></td>
</tr>
<tr>
<td>Bone metastases</td>
<td>5-8 (single fraction)</td>
</tr>
</tbody>
</table>

**Acute effects**

These result from depletion of rapidly dividing stem cells. In general, they are related to dose and treatment time but have little relation to fraction size. Even when severe, they are self limiting and recovery takes place provided the tolerance dose has not been exceeded.

*Nausea/vomiting:* The incidence of these is related to the volume of irradiation and the area involved, being more likely for abdominal or total body irradiation. Symptomatic measures include metoclopramide, or if more severe, 5HT3 antagonists such as ondansetron.

*Erythema:* The severity of this can be minimised by the use of high energy photon irradiation with its relative skin sparing. Moisturising cream can provide useful symptomatic relief from soreness or itching.

*Mucositis:* This is frequent when the volume includes the oropharynx or oesophagus. Symptomatic measures include the use of saline or hydrogen peroxide mouthwash. Careful attention to dental hygiene prior to, during and after radiotherapy is essential.

*Myelosuppression:* This occurs following wide field radiotherapy to areas including significant amounts of marrow. The elements predominantly affected are the white cells and platelets. The use of granulocyte
colony stimulating factor (GCSF) has been shown to reduce the tendency to neutropenia in patients undergoing craniospinal irradiation \(^{15}\) and may reduce the need for treatment interruptions.

**Alopecia:** This will be complete following 24 Gy prophylactic cranial irradiation, but regrowth occurs. Following the higher doses given for brain tumours, hair generally regrows after 45–50 Gy but after 55–60 Gy recovery may not be complete. The choice of radiation technique can be an important determinant of the extent and/or severity of alopecia.

### Subacute effects

**Central nervous system:** The 'somnolence syndrome' occurs in approximately 50% of children 4–8 weeks after 24 Gy prophylactic cranial irradiation for ALL. This is probably related to temporary demyelination. A similar syndrome, L’Hermitte’s syndrome may follow radiation to the upper spinal cord, e.g. following mediastinal radiotherapy for lymphoma. Following radiotherapy for brain tumours, children may experience a transient deterioration of neurological symptoms and signs which may require steroid therapy.

**Liver:** Radiation hepatopathy may occur 1–3 months following radiotherapy, and consists of hepatomegaly, jaundice, ascites, thrombocytopenia and elevated transaminases. A risk factor is the administration of actinomycin-D following hepatic irradiation. Long term dysfunction is rare but the risk is dose related.

**Lung:** Mild radiation pneumonitis consists of a dry cough and mild dyspnoea. The risk of pneumonitis is dose and radiation volume related. Radiation pneumonitis is the dose limiting toxicity for total body irradiation.

### Late effects

The incidence of late effects is related to the total radiation dose, but particularly to the fraction size. In this respect there is a dissociation between the risk of acute and the risk of late effects.

**Bone growth:** Impairment of bone growth can be one of the most obvious and distressing late effects. This can be particularly distressing when treating the head and neck region. The proliferative cells in the
Radiotherapeutic approaches

Epiphysial growth plate are exquisitely sensitive to radiation. Probert and Parker\textsuperscript{16} quantified axial skeletal growth arrest in a series of children receiving spinal irradiation for the treatment of medulloblastoma, ALL or Hodgkin’s disease. The series was updated by Willman\textsuperscript{17}. Age at time of treatment, radiation dose and volume are factors which have an impact on ultimate stature. There was evidence of a dose response effect, with a greater effect seen for a dose of $> 33$ Gy compared with $< 33$ Gy. Slipped femoral epiphysis, and avascular necrosis have also been reported following radiation to the hip. Abnormalities of craniofacial growth can cause significant cosmetic and functional deformity, including micrognathia leading to problems with dentition. Laboratory evidence suggests a dose response effect between 5 Gy and 35–40 Gy, and an intermediate effect of dose per fraction.

Careful consideration of the late orthopaedic effects of radiation are extremely important when planning radiotherapy. Epiphyses are excluded wherever possible.

**Central nervous system:** Radionecrosis is rare below 60 Gy, and generally occurs with a latency of 6 months to 2 years\textsuperscript{18}. It results from a direct effect on glial tissue. It occurs in approximately 50% of patients treated by interstitial implantation for recurrent brain tumours following prior radical external beam radiotherapy. The clinical effects of radionecrosis vary according to the site within the CNS and are most devastating in the spinal cord.

Necrotising leukoencephalopathy may be seen when cranial irradiation is followed by high dose methotrexate\textsuperscript{18}.

**Neuropsychological effects**—an IQ reduction of approximately 13 points is seen in children given 24 Gy prophylactic cranial irradiation compared with siblings\textsuperscript{19}. Following higher doses for brain tumours, in addition, an increased risk of learning and behaviour difficulties is seen. An important risk factor for the incidence of neuropsychological late effects is the age at diagnosis\textsuperscript{2}.

**Kidney:** Late effects on renal function are usually seen 2–3 years following a course of radiotherapy. The severity is related to the dose received, and when mild consists of hypertension. When more severe, following a higher dose, renal failure may ensue.

**Endocrine:** Endocrine deficiencies following radiotherapy are common. Of particular concern is the risk of growth hormone deficiency following pituitary irradiation\textsuperscript{20}. Following radiotherapy to the thyroid, the incidence of elevated TSH is 75% after 25–40 Gy.
Reproductive: In boys, the germinal epithelium is very sensitive to the effects of low dose irradiation. In adult males, transient oligospermia is seen after 2 Gy, but slow recovery can occur after 2–5 Gy. In girls, the oocytes are also sensitive. Subsequent pregnancy is rare but has been reported after 12 Gy whole body irradiation.

Tolerance of critical organs to radiotherapy

The tolerance of critical organs limits frequently the dose of radiation that can be given. The critical organs and their ‘tolerance doses’ are given in Table 2.

Chemotherapy/radiotherapy interactions

Interactions between radiation and chemotherapy are complex and poorly understood\textsuperscript{21}. Interactions can be exploited in order to attempt to improve disease free survival. Interactions have been classified into four mechanisms\textsuperscript{22}.

Spatial co-operation: Chemotherapy and radiotherapy are combined to exploit their differing roles in different anatomical sites. Examples are the use of radiation for local control of a primary, with chemotherapy for subclinical metastatic disease and the use of radiotherapy for the treatment of ‘sanctuary sites’, e.g. CNS prophylaxis for the treatment of ALL.

Additive effects: This involves increased tumour cell kill when the two modalities produce their effects by different mechanisms. This may be of value provided there are no overlapping toxicities, which necessitate a significant dose reduction of one or both modalities.

Enhancement: This may be regarded as ‘true interaction’. The combined effect of the two modalities is greater than would be expected

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### Table 2

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tolerance dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung</td>
<td>18</td>
</tr>
<tr>
<td>Kidney</td>
<td>15</td>
</tr>
<tr>
<td>Liver</td>
<td>20</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>50–55</td>
</tr>
</tbody>
</table>

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882 British Medical Bulletin 1996;52 (No. 4)
from a simple additive effect. Attempts to exploit enhancement have the problem of the potential for increased toxicity.

**Protection:** This is the use of drugs to preferentially protect normal tissues rather than tumours. There is experimental work suggesting that amifostine might be used to protect normal tissues from the effects of radiation.

When using combined modality therapy the aim is to improve the therapeutic ratio. Exploiting ‘spatial co-operation’ is frequent in many areas of paediatric oncology. However, when trying to exploit either the additive or enhancing effects of chemotherapy, it is frequently far from clear whether the therapeutic ratio has be improved.

Clinically important chemotherapy–radiotherapy interactions are often unpredictable and their mechanisms poorly understood. Actinomycin-D and cisplatin increase the slope of the radiation dose-response curve and actinomycin-D inhibits the repair of SLD.

Interactions include enhanced skin and mucosal toxicity when radiation is followed by actinomycin-D (the ‘recall phenomenon’), enhanced bladder toxicity when chemotherapy is combined with cyclophosphamide, enhanced CNS toxicity from combined radiation and methotrexate or cytosine arabinoside and the enhanced marrow toxicity from wide field irradiation and many myelotoxic chemotherapeutic agents. In the case of the effect of combined radiation and anthracyclines such as adriamycin on the heart, adriamycin has its effects on the myocytes and radiation on the vasculature.

### Current developments and future directions

#### Improved understanding of tumour biology

Knowledge of tumour biology may allow selective delay or avoidance of radiotherapy. The recognition that low grade astrocytomas may undergo prolonged periods of stability has led to the policy of observation rather than immediate radiotherapy, which will hopefully minimise late effects.

#### Radiosensitisers

At present there is no routine role for radiosensitisers in paediatric radiotherapy. The use of the radiosensitising effect of cisplatin is being explored in North American studies of brain stem glioma.
Cancer in children

**Targeted radiotherapy**

Metaiodobenzylguanidine (MIBG) conjugated with $^{131}$I has been used to deliver targeted radiotherapy for children with neuroblastoma. In a UK multicentre study of MIBG therapy in children with residual neuroblastoma after first line chemotherapy, a response rate of 30% was seen\(^24\). The use of ‘up front’ MIBG therapy incorporated into first line chemotherapy needs to be explored.

**Altered fractionation**

*Hyperfractionation:* A course of radical radiotherapy with a fraction size of 2 Gy can be ‘replaced’ by 1.2–1.3 Gy twice daily, allowing the total dose to be increased by 20–30%. This approach has been explored in the North American studies of hyperfractionation for brain stem glioma, but as yet there has been no evidence of an increased survival rate\(^25,26\).

*Accelerated fractionation:* This involves using the same fraction size, but shortening the overall treatment time, giving more than one fraction per day. This approach has been used as an empirical method of delivering concomitant split-course radiotherapy and chemotherapy for bulky pelvic Ewing’s sarcoma, avoiding the prolonged delay between chemotherapy cycles which occurs during ‘conventional’ radiotherapy\(^27\).

**Improved target volume definition**

Modern imaging allows better definition of tumour extent with the potential for more precise matching of radiation target volume to the tumour. In the case of low grade gliomas, the T2 image on MR scanning defines the tumour extent more precisely than the hypodense area on CT the image.

**Conformal/stereotactic radiotherapy**

Relating the target volume more precisely to the tumour extent, with 3D planning and treatment with non-coplanar beams has the potential for reducing late effects in children. At present, these techniques are routinely available in only a few centres within the UK.
Radiotherapeutic approaches

Radiotherapy localised with a cranial stereotactic frame, giving a single large fraction of either external beam radiotherapy from a linear accelerator or multiple ‘focused’ beams from a special cobalt unit, the ‘Gamma Knife’ is established in treatment of arterio-venous malformations (AVMs)\(^2\).

The role of fractionated stereotactic external beam radiotherapy using a relocatable stereotactic frame and employing a ‘standard’ fraction size of 1.8 Gy for small brain tumours is being explored.

References

Cancer in children


