

## 9. Paediatric cancer

### Background

Radiotherapy (RT) is an important modality of therapy in the local control of paediatric malignancies and the majority of paediatric tumours are radiosensitive. However, for many children, long-term survival comes at a price, namely the long-term effects of treatment. Long-term effects of radiotherapy include soft tissue hypoplasia, impaired bone growth, neuropsychological effects of irradiation of the central nervous system (CNS) and radiation-induced malignancy.

Currently, 40–50% of children with cancer receive radiotherapy as part of their initial treatment. It is extremely important that radiotherapy for children should be undertaken only in specialised centres associated with the Children's Cancer and Leukaemia Group (CCLG) paediatric oncology centres. The paediatric radiotherapy team should include a specialist paediatric therapy radiographer, specialist nurse and play specialist. The components of the paediatric multidisciplinary team are described in The Royal College of Radiologists' *Good practice guidance for paediatric radiology*.<sup>1</sup>

*Radiotherapy for children should only be carried out in designated departments associated with CCLG centres. The current document summarises typical dose-fractionation policies as applied in CCLG centres in the UK.*

### Leukaemia

The leukaemias account for the largest group of paediatric malignancies, with approximately 80% having acute lymphoblastic leukaemia (ALL). The remainder have acute non-lymphoblastic leukaemia (ANLL), usually acute myeloid leukaemia (AML) or, rarely, chronic myeloid leukaemia (CML). Currently more than 70% are long-term survivors. During the 1960s and 1970s, the routine use of prophylactic whole-brain radiotherapy (WBRT) and intrathecal methotrexate reduced the risk of CNS relapse to less than 10%. In current protocols, the use of WBRT is no longer standard but may be employed for patients who present with CNS involvement.<sup>2</sup>

#### Recommendation

##### **Whole brain radiotherapy childhood leukaemia:**

24 Gray (Gy) in 15 fractions of 1.6 Gy daily over 3 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

Boys who suffer a testicular relapse are treated with testicular radiotherapy, generally with electrons, encompassing a clinical target volume (CTV) which includes both testes, scrotum and the inguinal canal super-laterally as far as the deep inguinal ring.<sup>4</sup>

#### Recommendation

##### **Testicular irradiation in childhood leukaemia:**

24 Gy in 12 fractions of 2.0 Gy daily over 2.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Total body irradiation (TBI)

As in the treatment of adults with haematological malignancies, TBI is an important technique usually used together with high-dose cyclophosphamide (cyclo-TBI) as the conditioning regimen prior to bone marrow transplantation (BMT). Individual techniques for TBI have evolved in different departments, often depending on availability of treatment machines. TBI dosimetry is usually based on *in vivo* measurements. For such a large and complex target volume, it is not feasible to adhere to the International Commission on Radiation Units and Measurements (ICRU) 50 guidelines of a range of -5% to +7%; a range of -10% to +10% is more realistic.<sup>5-7</sup>

For children with ALL, many centres advise a cranial boost in addition to the TBI with the aim of reducing the risk of CNS relapse.<sup>8</sup>

### Recommendations

#### **TBI in childhood leukaemia:**

14.4 Gy in 8 fractions of 1.8 Gy twice daily with a minimum interfraction interval of 6 hours over 4 days (Level C)

#### **Cranial boost where indicated after TBI:**

5.4 Gy in 3 fractions over 3 days (Level D)

#### **TBI for bone marrow transplant (BMT) in benign haematological disorders, for example, Fanconi's anaemia and thalassaemia:**

2-3 Gy single dose (Level D)

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## Hodgkin lymphoma

The survival rate for children with Hodgkin lymphoma is approximately 90%. In current protocols, the aims are to maintain this good overall survival rate and reduce long-term effects.<sup>9-11</sup>

### Recommendations

#### **Hodgkin lymphoma: sites of initial involvement:**

19.8 Gy in 11 fractions over 2.2 weeks. Where there is significant residual disease (Level B)

#### **Hodgkin lymphoma: residual disease following chemotherapy or bulky sites:**

Boost of 10 Gy in 5 fractions over 1 week (Level B)

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## Neuroblastoma

The role of external beam radiotherapy for patients with 'bad risk' disease (for example, aged greater than one year with stage 4 disease at presentation) is to maximise the probability of local tumour control following surgical resection of the primary tumour.<sup>12-14</sup>

### Recommendation

#### **Neuroblastoma: postoperative radiotherapy to the tumour bed:**

21 Gy in 14 fractions over 3 weeks (Level B)

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## Wilms' tumour (nephroblastoma)

In Europe, the series of International Society of Paediatric Oncology (SIOP) studies have been based on preoperative chemotherapy to 'downstage' the primary, reducing the surgical morbidity, particularly the number who have tumour rupture at surgery and the number who require flank radiotherapy. Initial treatment is with preoperative chemotherapy with actinomycin-D and vincristine, with delayed nephrectomy after six weeks of preoperative chemotherapy. Postoperative adjuvant therapy is based on subsequent pathological staging and allocation of risk status (good risk versus intermediate risk versus poor risk histology).

Postoperative chemotherapy is given using the drugs vincristine, actinomycin D and doxorubicin, the number of drugs and duration are dependent upon the staging.

Postoperative flank radiotherapy is employed for stage III patients, that is, those with incompletely resected primary tumours, pre- or perioperative tumour rupture or histologically involved lymph nodes. Patients with gross pre- or perioperative tumour rupture or disseminated intra-abdominal disease should receive whole abdominal radiotherapy.<sup>15</sup> Patients with lung metastases who do not achieve a complete response to chemotherapy should receive whole lung radiotherapy.<sup>16</sup>

### Recommendations

#### **Wilms tumour: postoperative radiotherapy to flank:**

**Intermediate risk:** 14.4 Gy in 8 fractions of 1.8 Gy daily over 1.5 weeks (Level B)

**High risk:** 25.2 Gy in 14 fractions of 1.8 Gy over 2 weeks (Level B)

#### **Wilms tumour: whole abdominal radiotherapy**

21 Gy in 14 fractions of 1.5 Gy over 2 weeks (Level B)

#### **Boost to macroscopic disease or involved nodes:**

10.8 Gy in 6 fractions of 1.8 Gy over 1.5 weeks (Level B)

#### **Wilms tumour: whole lung radiotherapy**

15 Gy in 10 fractions of 1.5 Gy over 2 weeks (Level B)

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## Rhabdomyosarcoma

The basis of treatment has generally involved the use of intensive chemotherapy with the aim of improving survival, and reducing the use of local therapy with surgery and/or radiotherapy, thus minimising long-term effects. Treatment is stratified according to risk groups based on parameters such as histological subtype (embryonal versus alveolar histology), stage of disease and primary tumour site. Patients in the 'low-risk' category, that is, those with localised tumours which are microscopically completely resected, are treated with chemotherapy using actinomycin-D and vincristine for nine weeks.<sup>17-19</sup> Standard risk tumours are those which are locally more extensive but at selected favourable sites, for example, the vagina, uterus or paratestis, and are treated with ifosfamide, vincristine and actinomycin-D. Poor responders switch to a six-drug combination. High-risk tumours include other incompletely resected tumours, including all those arising in parameningeal sites (nasopharynx, middle ear) and those with involved lymph nodes. These are treated with further chemotherapy.

### Recommendations

#### **Embryonal rhabdomyosarcoma:**

##### **Post-chemotherapy, no surgery:**

41.4 Gy in 23 fractions of 1.8 Gy following complete response to chemotherapy and 50.4 Gy in 28 fractions of 1.8 Gy for incomplete response (Level B)

Consider boost of 5.4 Gy in 3 fractions of 1.8 Gy for large tumours and/or poor response to chemotherapy

##### **Postoperative:**

36 Gy in 20 fractions of 1.8 Gy (Level B)

#### **Alveolar rhabdomyosarcoma:**

##### **Post-chemotherapy, no surgery:**

50.4 Gy in 28 fractions of 1.8 Gy (Level B)

Consider boost of 5.4 Gy in 3 fractions of 1.8 Gy for large tumours and/or poor response to chemotherapy

##### **Postoperative:**

41.4 Gy in 23 fractions of 1.8 Gy (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### **Ewings sarcoma/peripheral primitive neuroectodermal tumour (PPNET)**

Initial treatment is with chemotherapy in conjunction with the appropriate use of local therapy. The decision as to whether surgery, radiotherapy or both should be employed for local control of the primary tumour demands careful multidisciplinary discussion. In previous series, patients' survival has been better following local treatment with surgery compared with radiotherapy alone. However, these series are confounded by selection bias with patients with smaller tumours selected for surgery.<sup>20,21</sup>

### Recommendations

#### Ewings and PPNET:

##### Phase 1 and postoperative volume:

45 Gy in fractions of 1.8 Gy over 5 weeks (Level B)

##### Phase 2 for macroscopic disease:

9.6 Gy in fractions of 1.8–2.0 Gy (Level B)

#### Ewings and PPNET:

##### Whole lung radiotherapy:

15 Gy in 10 fractions over 2 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Central nervous system tumours

### Low-grade astrocytoma

These comprise the most common group of paediatric CNS tumours. Modern management is based on the recognition that low-grade gliomas may undergo long periods of 'quiescence' even when not completely resected. The current five-year survival rate is 85%, but late relapse is not uncommon.

Treatment is initially with surgical resection, as complete as is considered safe.

In the recently closed SIOP Low-Grade Glioma (LGG2) study, those over the age of seven were treated with radiotherapy. Those aged seven or under received chemotherapy with the aim of delaying radiotherapy.<sup>22</sup>

### Recommendation

#### Low-grade astrocytoma:

54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

For patients who present with spinal cord primary low-grade glioma, the management policy will be similar.

### Recommendation

#### Low-grade spinal astrocytoma:

50.4 Gy in 28 fractions of 1.8 Gy over 5.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### High-grade astrocytoma

Unlike adults, high-grade astrocytomas are uncommon in childhood. However, in common with adults, the outlook is generally poor. Survival is currently approximately 20% at five years. Current management is based on surgical resection and postoperative chemoradiotherapy with temozolomide.<sup>23</sup>

#### Recommendation

##### High-grade astrocytoma:

**Under 14 years:** 54 Gy in 30 fractions over 6 weeks (Level B)

**Over 14 years:** 60 Gy in 30 fractions over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Ependymoma

The overall five-year survival rate is approximately 50–60%. In the majority of studies, prognostic factors include tumour grade and extent of resection. The predominant site of relapse is within the local tumour bed. The majority of collaborative groups now recommend an increased radiotherapy dose (59.4 Gy with conformal techniques).<sup>24</sup>

#### Recommendation

##### Ependymoma:

59.4 Gy in 33 fractions in 6.5 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

### Medulloblastoma/primitive neuroectodermal tumour (PNET)

Medulloblastoma is a primitive neuronal tumour which arises in the cerebellum. It is notable for its propensity for metastatic spread via the craniospinal fluid (CSF) and its radiosensitivity. PNET arises elsewhere in the CNS, usually the supratentorial cerebral cortex, where they are referred to as supratentorial PNET (StPNET). PNET arising in the pineal area are referred to as pineoblastoma.

Standard therapy for medulloblastoma/PNET is initial maximal surgical resection followed by craniospinal radiotherapy and a 'boost' to the primary site.

Current studies are based on the allocation of risk status. Standard-risk disease refers to non-metastatic medulloblastoma with complete or near-complete surgical resection. High-risk disease includes patients with medulloblastoma with metastases or postsurgical residue and StPNET.

It is standard practice to employ adjuvant chemotherapy (vincristine, CCNU, cisplatin) following radiotherapy for patients with standard-risk disease and more intensive chemotherapy for high-risk disease.<sup>25–27</sup>

### Recommendations

#### Medulloblastoma/PNET:

##### Standard-risk craniospinal:

23.4 Gy in 13 fractions over 2.5 weeks (Level B) followed by boost to tumour bed or whole posterior fossa

30.6 Gy in 17 fractions in 3.5 weeks (Level B)

##### High-risk medulloblastoma and StPNET craniospinal

36.0 Gy in 20 fractions over 4 weeks (Level B)

39.6 Gy in 22 fractions over 4.4 weeks (St Jude's regimen for M2–3) (Level B)

Followed by boost to primary site to a total of 54.0–55.8 Gy in 1.8 Gy fractions (Level B)

Boost to sites of metastases to a total of 50.4 Gy (spinal) and 54–55.8 Gy (intracranial) in 1.8 Gy fractions (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Intracranial germ cell tumours

Intracranial germ cell tumours account for approximately 30% of paediatric germ cell tumours. For germinoma, although in the past craniospinal radiotherapy has been standard, future trials will explore the role of chemotherapy and whole ventricular radiotherapy. Patients with non-germinoma receive platinum based chemotherapy and radiotherapy, either focal for non-metastatic disease or craniospinal for metastatic disease.<sup>28,29</sup>

### Recommendations

#### Germinoma – craniospinal radiotherapy, no chemotherapy:

24 Gy in 15 fractions over 3 weeks followed by boost to primary site (Level B)

16 Gy in 10 daily fractions over 2 weeks (Level B)

#### Germinoma – post-chemotherapy: whole ventricular radiotherapy:

24 Gy in 15 fractions over 3 weeks followed by boost to residual disease (Level B)

16 Gy in 10 daily fractions over 2 weeks (Level B)

#### Non-germinomatous tumours – primary tumour:

54 Gy in 30 fractions over 6 weeks (Level B)

#### Meningeal metastases – craniospinal axis:

30 Gy in 20 fractions over 4 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>



## Brain stem glioma

This includes tumours arising in the midbrain, pons and medulla. Historically they were regarded as a single entity. However, it is now clear that they can be subdivided into focal (5–10%), dorsal exophytic (10–20%), cervico-medullary (5–10%) and diffuse intrinsic tumours (75–85%).

The majority of children with brain stem gliomas have diffuse intrinsic pontine glioma (DIPG), which are usually high-grade astrocytomas. Their prognosis is very poor with a median survival of approximately nine months and very few long-term survivors.<sup>30</sup>

### Recommendation

#### Brain stem glioma:

54 Gy in 30 fractions over 6 weeks (Level B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-based Medicine.<sup>3</sup>

## Further reading

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