11 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 the price of long-term effects of treatment. Long-term effects of radiotherapy include soft tissue hypoplasia, impaired bone growth, endocrine dysfunction, impaired fertility, 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. 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 RCR *Good practice guidance for paediatric radiology*.[1]

Wherever possible, parents of children requiring radiotherapy should be offered the opportunity for their child to have treatment within an appropriate National Cancer Research Institute (NCRI) portfolio or international trial.

Radiotherapy for children should only be carried out in designated departments associated with Children's Cancer and Leukaemia Group (CCLG) principal treatment 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 leukaemias, usually acute myeloid leukaemia (AML) or, rarely, chronic myeloid leukaemia (CML). Currently more than 85% with ALL and 65% with AML are long-term survivors.

In current protocols, WBRT may be employed for patients with relapsed or refractory CNS involvement, either alone, as detailed below, or delivered as a boost (see total body irradiation section) prior to total body irradiation.[2,3]

11
Paediatric cancer

Recommendation

Whole-brain radiotherapy in 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.[4]

Children with a testicular relapse may be treated with testicular radiotherapy, generally using orthovoltage or electrons, encompassing a clinical target volume (CTV) that includes both testes, the scrotum and the inguinal canal supero-laterally as far as the deep inguinal ring, either alone, as detailed below, or delivered as a boost (see total body irradiation section) prior to total body irradiation.[5]

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.[4]

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 or etoposide as the conditioning regimen prior to bone marrow transplantation (BMT).[6,7] Individual techniques for TBI have evolved in different departments due to a number of factors including available equipment and bunker size. TBI planning often utilises CT in addition to *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.[7–10]

11

Paediatric cancer

Recommendations

TBI in childhood leukaemia:

- 13.2–14.4 Gy in 8 fractions of 1.65–1.8 Gy twice daily, with a minimum interfraction interval of 6 hours over 4 days (Level C)
- 12 Gy in 6 fractions of 2 Gy twice daily with a minimum interfraction interval of 6 hours over 3 days (Level C)

Cranial boost where indicated (given in the days prior to TBI):

- 5.4–6 Gy in 3–4 fractions of 1.5–1.8 Gy daily over 3 days (Level C)

Testicular boost where indicated (given in the days prior to TBI):

- 5.4–6 Gy in 3–4 fractions of 1.5–1.8 Gy daily over 3 days (Level C)
- 4 Gy single fraction over 1 day (Level C)

TBI for reduced-intensity cord transplant or benign haematological disorders (eg Fanconi's anaemia and thalassaemia):

- 2–4 Gy single dose (Level C)

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.[4]

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.[11–13] Patients are stratified into treatment risk groups (TL-1, TL-2 and TL-3) based on stage and risk factors such as disease bulk and erythrocyte sedimentation rate (ESR) levels, as defined in the recent international EuroNet pHL-C2 study.

Typically patients are selected for radiotherapy if their disease demonstrates an inadequate response on 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography computed tomography (PET-CT) early response reassessment after initial chemotherapy (2 cycles of OEPA).[14] An involved-site approach encompassing all sites initially involved is recommended, with an additional boost recommended for TL-2 and TL-3 patients if there is residual avid disease at the end of chemotherapy on the late-response assessment FDG PET-CT scan.

The EuroNet pHL-C2 phase III trial investigated a strategy of chemotherapy intensification (DECOPDAC) and response-adapted radiotherapy strategy for TL-2 and TL-3 patients. Only FDG PET-positive sites of disease at the end of chemotherapy (late-response assessment) are irradiated to a dose of 28.8 Gy in 16 fractions of 1.8 Gy daily over 3.5 weeks. The results of this trial are expected in the next 6–12 months and if positive the experimental radiotherapy strategy will be adopted as the standard of care for patients receiving DECOPDAC chemotherapy.

11
Paediatric cancer

Given the current risk-stratified approach, which looks to limit the use of radiotherapy as part of initial treatment, many patients who relapse may never have received radiotherapy before or may relapse at sites previously not irradiated. For these patients, radiotherapy should be considered as part of the relapsed salvage treatment strategy, but this should be carefully tailored taking into consideration any previous radiotherapy and the potential toxicity from the required involved-site radiotherapy.[15]

Recommendations

Hodgkin lymphoma: upfront treatment of initial involved sites:

• 19.8 Gy in 11 fractions of 1.8 Gy daily over 2.5 weeks (Level B)

Hodgkin lymphoma: residual FDG-avid disease following completion of chemotherapy:

• Boost of 10 Gy in 5 fractions of 2 Gy daily over 1 week (Level B)

Refractory/relapsed Hodgkin lymphoma at radiotherapy naive sites:

• 30.6 Gy in 17 fractions of 1.8 Gy daily over 3.5 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.[4]

Neuroblastoma

Patients with neuroblastoma are risk-stratified at presentation by age, stage and molecular pathology. External beam radiotherapy to the primary tumour bed is indicated for all patients with high-risk (including metastatic) disease and selected patients with intermediate-risk disease. The intent is to maximise the probability of local tumour control following induction chemotherapy, surgical resection of the primary tumour and high-dose chemotherapy.[16–18] The role of dose escalation to 36 Gy in the context of macroscopic residual disease is currently under investigation within the SIOPEN HR-NBL2 phase III international trial.

Recommendations

Neuroblastoma: postoperative radiotherapy to the tumour bed:

• 21 Gy in 14 fractions of 1.5 Gy daily over 2.5 weeks (Level B) or
• 21.6 Gy in 12 fractions of 1.8 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.[4]

11
Paediatric cancer

Wilms' tumour (nephroblastoma)

In Europe, the International Society of Paediatric Oncology (SIOP) UMBRELLA study approach utilises preoperative chemotherapy to 'downstage' the primary and reduce the surgical morbidity, the risk of tumour rupture at surgery and the number who require adjuvant flank radiotherapy. After 6 weeks of initial preoperative actinomycin-D and vincristine (VA) chemotherapy, patients proceed to delayed nephrectomy. Postoperative adjuvant therapy is based on postoperative pathological staging and allocation of risk status (good risk versus intermediate risk versus poor risk histology).

Postoperative chemotherapy again uses vincristine, actinomycin-D, with the duration and the requirement for other drugs dependent upon the staging and risk grouping.

Postoperative flank radiotherapy is employed for stage III patients, including 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 and pelvic radiotherapy.[19] Patients with lung metastases who do not achieve a complete response to chemotherapy should receive whole-lung radiotherapy.[20]

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, stage II (except blastemal subtype*) and stage III (all histology):** 25.2 Gy in 14 fractions of 1.8 Gy daily over 2.5 weeks (Level B)
- **Boost to macroscopic residual disease after surgery (intermediate risk):** delivering a total dose of 25.2 Gy in 14 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 10.8 Gy in 6 fractions of 1.8 Gy daily over 1.5 weeks after receiving 14.4 Gy (Level B)
- **Boost to macroscopic residual disease after surgery (high risk):** delivering a total dose of 36 Gy in 20 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 10.8 Gy in 6 fractions of 1.8 Gy daily over 1.5 weeks after receiving 25.2 Gy (Level B)

Wilms' tumour: whole-abdominal and pelvic radiotherapy:

Depending upon histopathological risk group:

- **Intermediate risk:** 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks (Level B)
- **High risk:** 19.5 Gy in 13 fractions of 1.5 Gy daily over 2.5 weeks (Level B) ± boost to flank delivering a total dose of 25.2 Gy in 14 fractions of 1.8 Gy daily over 2.5 weeks (or equivalent)

**The poor prognosis of blastemal subtype is caused by metastases and not by increased local recurrence, therefore radiotherapy to primary tumour bed in stage II disease is not recommended.*

11
Paediatric cancer

Recommendations (contd)

Wilms' tumour: whole-lung radiotherapy:

- **Intermediate risk:** 12 Gy in 8 fractions of 1.5 Gy daily over 1.5 weeks (Level B)
- **High risk:** 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks (Level B)
- For infants (<1 year) a lower dose per fraction (1.2–1.5 Gy daily) may be considered on an individualised basis. If multiple areas require treatment, simultaneous treatment to avoid overlap of fields is preferable.

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.[4]

Rhabdomyosarcoma (RMS)

The basis of treatment involves multimodality treatment with induction chemotherapy followed by local therapy utilising surgery and/or radiotherapy.[21–24] Treatment is stratified according to risk groups based on parameters such as PAX01 fusion gene status (positive versus negative), stage of disease, age and primary tumour site. High-risk RMS are treated with 9 cycles of induction ifosfamide, vincristine and actinomycin-D (IVA) chemotherapy, and very high risk (including metastatic disease) receive similar chemotherapy with 4 cycles also incorporating doxorubicin; both high-risk and very high-risk patients receive low-dose maintenance chemotherapy (6 months and 12 months respectively) after the completion of the induction phase. Standard-risk patients receive only 5 cycles of IVA and 4 cycles of VA if they are also having radiotherapy, and patients in the low-risk category, with localised tumours at a favourable site that are microscopically completely resected, receive only 8 cycles of actinomycin-D and vincristine chemotherapy for 22 weeks.[18–20]

It is important to ensure that the choice of local therapy offers the most optimal local control, carefully balanced with the risk of long-term effects in the decision-making process. The benefits of dose escalation for tumours at unfavourable sites and in adults (both adjuvant and primary radiotherapy) are being explored in the FaR-RMS trial currently open to recruitment.

Brachytherapy may be considered for very carefully selected patients such as those with localised embryonal bladder/prostate and female genital tract RMS.[25,26] Such patients should be referred to a specialist centre with experience in this type of treatment.

In the metastatic setting, radical irradiation of all metastatic sites may confer a survival advantage in selected patients, usually with only 1 or 2 metastatic sites.[27] The role of metastatic radiotherapy in the wider setting is currently being investigated within the FaR-RMS trial.

11
Paediatric cancer

Recommendations

Unresectable disease, definitive radiotherapy:

- 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks, if incomplete response, given at 2 dose levels: 41.4 Gy in 23 fractions of 1.8 Gy daily to disease at presentation, followed by 9 Gy in 5 fractions of 1.8 Gy daily boost to residual disease (Level B)
- Can consider boost, delivering a total dose of 55.8 Gy in 31 fractions (an additional 5.4 Gy in 3 fractions of 1.8 Gy daily) for large tumours with poor response to induction chemotherapy (Level B)

or

- 41.4 Gy in 23 fractions of 1.8 Gy daily over 4.5 weeks following complete response to induction chemotherapy (Level B)

Resectable disease, pre- or postoperative radiotherapy:

- 41.4 Gy in 23 fractions of 1.8 Gy daily over 4.5 weeks
- Boost to macroscopic residual disease after surgery: delivering a total dose of 50.4 Gy in 28 fractions of 1.8 Gy per fraction (or equivalent), for example an additional 9 Gy in 5 fractions of 1.8 Gy daily over 1 week after receiving 41.4 Gy (Level B)

Definitive radiotherapy for metastatic sites:

- Bone, nodal and soft-tissue metastases: 41.4 Gy in 23 fractions of 1.8 Gy daily (or equivalent)
- Whole-lung radiotherapy: 15 Gy in 10 fractions of 1.5 Gy daily
- Whole-abdominal and pelvic radiotherapy: 24 Gy in 16 fractions of 1.5 Gy daily (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.[4]

Ewing sarcoma

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.[28,29] In some situations, definitive radiotherapy may be more appropriate than surgery, particularly in cases requiring extensive resection at pelvic or spinal locations.[30,31]

The upcoming Inter-Ewing-1 trial will evaluate the role of dose escalation for definitive radiotherapy and the optimal dose for postoperative radiotherapy. Centres are encouraged to consider patients for the trial as appropriate when the trial is open to recruitment.

11

Paediatric cancer

Recommendations

Preoperative radiotherapy:

- 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks (Level B)
- 45 Gy in 25 fractions of 1.8 Gy daily over 5 weeks can be considered, particularly if there are concerns about organ tolerance or wound healing

Postoperative radiotherapy:

- 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks, delivered in 2 phases: 45 Gy in 25 fractions followed by a boost of 9 Gy in 5 fractions (Level B)

Definitive radiotherapy:

- 54 Gy in 30 fractions of 1.8 Gy daily
- A boost of 5.4 Gy in 3 fractions of 1.8 Gy daily sequentially, or delivering up to 60 Gy as a simultaneous integrated boost may be considered (Level B)

Whole-lung radiotherapy:

- <14 years of age: 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks
- ≥14 years of age: 18 Gy in 12 fractions of 1.5 Gy 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.[4]

Central nervous system tumours

Low-grade glioma

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 5-year survival rate is 85%, but late relapse is not uncommon.

Treatment is initially with surgical resection, as complete as is considered safe. Systemic therapy is increasingly being used. Decision on the sequencing of systemic therapy and timing of radiotherapy should be made on an individualised basis based on burden of symptoms, age, site and extent of tumour. In general, radiotherapy is delayed or avoided where possible, especially in NF1 and young patients.[32–34]

11
Paediatric cancer

Recommendation

Low-grade glioma:

• 50.4–54 Gy in 28–30 fractions of 1.8 Gy daily over 5.5–6 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.[4]

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

Recommendation

Low-grade spinal glioma:

• 50.1–50.4 Gy in 28–30 fractions of 1.67–1.8 Gy daily over 5.5–6 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.[4]

High-grade glioma

Unlike in adults, high-grade gliomas are uncommon in childhood. However, in common with adults, the outlook is generally poor. Survival is currently approximately 20% at 5 years. Current management is based on surgical resection and postoperative chemoradiotherapy with temozolomide.[24]

Diffuse midline gliomas (DMG), H3 K27M-mutant, arising in the midbrain, pons, medulla and thalami, are considered high-grade glioma. Their prognosis is very poor, particularly those arising in the brainstem, with a median survival of approximately 9 months and very few long-term survivors.[35] Urgent upfront radiotherapy is the mainstay of treatment for these patients for symptom control. Hypofractionation can be used to minimise time spent on treatment for patients with brainstem tumours and those with poor performance status.[36] Reirradiation can be considered if there has been a time interval (usually at least 6 months) between the end of initial radiotherapy treatment and disease progression.[37]

11

Paediatric cancer

Recommendations

High-grade glioma:

• 54–59.4 Gy in 30–33 fractions of 1.8 Gy daily over 6 weeks (Level B)

Diffuse midline glioma of the brainstem:

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

or

• 39 Gy in 13 fractions of 3 Gy daily over 2.5 weeks (Level B)

Diffuse midline glioma of the brainstem – reirradiation:

• 20 Gy in 10 fractions of 2 Gy daily given 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.[4]

Ependymoma

The overall 5-year survival rate is approximately 50–60%. Prognostic factors include tumour grade and extent of resection, with the predominant site of relapse within the local tumour bed. The majority of collaborative groups now recommend the use of a higher radiotherapy dose (59.4 Gy with highly conformal techniques) taking care to limit the dose to the brainstem and other adjacent critical structures.[38,39]

Recommendations

Intracranial ependymoma:

• 59.4 Gy in 33 fractions of 1.8 Gy daily over 6.5 weeks (Level B)
• 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks in very young children <18 months, poor neurological status or multiple surgeries

Spinal ependymoma:

• 50.4–54 Gy in 28–30 fractions of 1.8 Gy daily over 5.5–6 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.[4]

11
Paediatric cancer

Medulloblastoma

Medulloblastoma is an embryonal tumour of the CNS, which arises in the cerebellum. It is notable for its propensity for metastatic spread via the craniospinal fluid (CSF) and its radiosensitivity. Embryonal tumours can arise elsewhere in the CNS and are now referred to as CNS embryonal tumours, with those arising in the pineal area defined as pineoblastoma.

Standard therapy for medulloblastoma, other CNS embryonal tumours and pineoblastoma 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.[40,41] Standard-risk disease refers to non-metastatic medulloblastoma with complete or near complete surgical resection.

High-risk disease includes patients with medulloblastoma with large cell histology, metastases or postsurgical residue.

It is standard practice to employ adjuvant chemotherapy (vincristine, CCNU, cisplatin and/or cyclophosphamide, vincristine) following radiotherapy for patients with standard-risk and high-risk disease, although more intensive chemotherapy is utilised in some high-risk disease protocols, including one of the arms in the current SIOP high-risk medulloblastoma study.[42–44]

Recommendations

Medulloblastoma, CNS embryonal tumours and pineoblastoma:

Standard-risk craniospinal:

- 23.4 Gy in 13 fractions of 1.8 Gy daily over 2.5 weeks (Level B) followed by boost of 30.6 Gy in 17 fractions of 1.8 Gy daily in 3.5 weeks to tumour bed or whole posterior fossa to a total dose of 54 Gy (Level B)

High-risk craniospinal:

- 36.0 Gy in 20 fractions of 1.8 Gy daily over 4 weeks (Level B)
- 39.6 Gy in 22 fractions of 1.8 Gy daily over 4.5 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 fractions of 1.8 Gy daily (Level B)
- Boost to sites of metastases to a total of 45–50.4 Gy (spinal) and 54–55.8 Gy (intracranial) fractions of 1.8 Gy daily (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.[4]

Intracranial germ cell tumours

Intracranial germ cell tumours (GCT) account for approximately 30% of paediatric GCT. Localised disease for both germinoma and non-germinoma GCT refers to unifocal or bifocal disease involving only the pineal and/or the pituitary/suprasellar region.

11

Paediatric cancer

For germinoma, craniospinal radiotherapy is no longer the standard of care for all stages, with initial chemotherapy and whole-ventricular radiotherapy ± boost now offered to patients with localised disease.[45]

Patients with non-germinoma receive platinum-based chemotherapy and radiotherapy, either whole-ventricular radiotherapy with focal boost for non-metastatic disease[46] or craniospinal for metastatic disease.[47]

Recommendations

Germinoma, post-chemotherapy, localised disease – whole-ventricular radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks
- Bifocal tumours, and those localised to suprasellar or pineal regions not achieving complete radiological response (CR) with induction chemotherapy, should receive a further boost to residual disease of 16 Gy in 10 fractions of 1.6 Gy daily over 2 weeks, delivering a total dose of 40 Gy (Level B)

Germinoma, localised with no chemotherapy or metastatic disease – craniospinal radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks followed by boost to primary and metastatic sites of 16 Gy in 10 daily fractions of 1.6 Gy daily over 2 weeks (Level B)

Non-germinomatous GCT, localised disease – whole-ventricular radiotherapy:

- 24 Gy in 15 fractions of 1.6 Gy daily over 3 weeks followed by a boost to primary tumour to a total dose of 54 Gy, in fractions not exceeding 1.8 Gy daily (Level B)
- A simultaneous integrated boost approach can be used to treat the primary site(s) to 27 Gy in 15 fractions (1.8 Gy daily) concurrently with the whole ventricles receiving 24 Gy in 15 fractions (1.6 Gy daily). This is followed by a boost of 27 Gy in 15 fractions to the primary site(s) only, with a total dose to the primary site(s) of 54 Gy in 30 fractions of 1.8 Gy daily over 6 weeks.

Non-germinomatous GCT, meningeal metastases – craniospinal radiotherapy:

- 30 Gy in 20 fractions of 1.5 Gy daily over 4 weeks (Level B). Boost to primary and metastatic sites of 24 Gy in 15 fractions (intracranial) or 20.8 Gy in 13 fractions (spinal) of 1.6 Gy daily over 2.5–3 weeks, delivering a total dose of 54 Gy intracranially and 50.8 Gy to involved spinal sites
- If more than two-thirds of spine is involved with macroscopic disease, the total dose should be limited to 45 Gy (ie additional boost of 15 Gy in 10 fractions of 1.5 Gy daily over 2 weeks)

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.[4]

11
Paediatric cancer

Craniopharyngioma

Radiotherapy is usually recommended when tumour resection is incomplete. In select cases where morbidity of radiation outweighs the benefits, such as in very young children with minimal residual disease, it may be appropriate to defer radiotherapy until there is clear tumour progression.[48] Experience with doses of 50–54 Gy, with fraction sizes not exceeding 1.8 Gy daily, have been reported internationally.[49,50] However, there remains a lack of evidence to demonstrate that a higher radiation dose improves local control rate. Given concern over the risk of optic neuropathy and brainstem toxicity, particularly for young patients with this type of benign tumour, a cautious approach to treat to a dose of 50.4 Gy in 28 fractions of 1.8 Gy daily over 5.5 weeks may be favoured.

Recommendation

• 50.1–54 Gy in 28–30 fractions of 1.67–1.8 Gy daily over 5.5–6 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.[4]

Further reading

i. Boterberg T, Dieckmann K, Gaze M (eds). *Radiotherapy and the cancers of children, teenagers and young adults: radiotherapy in practice*. Oxford: Oxford University Press, 2020.

ii. Constine LS, Tarbell NJ, Halperin EC (eds). *Pediatric radiation oncology*. 6th revised edition. Philadelphia: Lippincott Williams & Wilkins, 2016.

iii. Mandeville HC. Principles of paediatric radiation oncology (chapter 21). In: P Hoskin. *External beam therapy*. Third edition. Oxford: Oxford University Press, 2019.

i. Lavan NA, Saran FH, Oelfke U, Mandeville HC. Adopting advanced radiotherapy techniques in the treatment of paediatric extracranial malignancies: challenges and future directions. *Clin Oncol (R Coll Radiol)* 2019 Jan; **31**(1): 50–57. doi:10.1016/j.clon.2018.08.020.

ii. Thorp N, Taylor RE. Management of central nervous system tumours in children. *Clin Oncol (R Coll Radiol)* 2014; **26**(7): 438–445.

iii. www.cclg.org.uk/member-area/treatment-guidelines

References

1. Gaze MN. Good practice guide for paediatric radiotherapy. *Clin Oncol (R Coll Radiol)* 2019; **31**(3): 139–41.

2. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 2008; **9**(3): 257–68.

3. CCLG Relapsed ALL guideline. 2021 (v1.3 Jan 2022). www.cclg.org.uk/member-area/treatment-guidelines/leukaemias

4. www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009 (last accessed 28/11/2023).

5. Bowman WP, Aur RJ, Hustu HO, Rivera G. Isolated testicular relapse in acute lymphocytic leukemia of childhood: categories and influence on survival. *J Clin Oncol* 1984; **2**(8): 924–9.

11
Paediatric cancer

6. Peters C, Dalle JH, Locatelli F *et al*. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. *J Clin Oncol* 2021; **39**(4): 295–307.
7. Hoeben BAW, Pazos M, Seravalli E *et al*. ESTRO ACROP and SIOPE recommendations for myeloablative total body irradiation in children. *Radiother Oncol* 2022; **173**: 119–33.
8. Jones D. ICRU report 50. Prescribing, recording and reporting photon beam therapy. *Med Phys* 1994; **21**(6): 833–4.
9. Cosset JM, Girinsky T, Malaise E, Chaillet MP, Dutreix J. Clinical basis for TBI fractionation. *Radiother Oncol* 1990; **18** Suppl 1: 60–7.
10. Gerrard GE, Vail A, Taylor RE *et al*. Toxicity and dosimetry of fractionated total body irradiation prior to allogeneic bone marrow transplantation using a straightforward radiotherapy technique. *Clin Oncol (R Coll Radiol)* 1998; **10**(6): 379–83.
11. Ruhl U, Albrecht M, Dieckmann K *et al*. Response-adapted radiotherapy in the treatment of pediatric Hodgkin's disease: an interim report at 5 years of the German GPOH-HD 95 trial. *Int J Radiat Oncol Biol Phys* 2001; **51**(5): 1209–18.
12. Frew JA, Lewis J, Lucraft HH. The management of children with lymphomas. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 11–8.
13. Mauz-Korholz C, Metzger ML, Kelly KM *et al*. Pediatric Hodgkin lymphoma. *J Clin Oncol* 2015; **33**(27): 2975–85.
14. Mauz-Korholz C, Landman-Parker J, Balwierz W *et al*. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. *Lancet Oncol* 2022; **23**(1): 125–37.
15. Daw S, Hasenclever D, Mascarin M *et al*. Risk and response adapted treatment guidelines for managing first relapsed and refractory classical Hodgkin lymphoma in children and young people. Recommendations from the EuroNet Pediatric Hodgkin Lymphoma Group. *Hemasphere* 2020; **4**(1): e329.
16. Wolden SL, Gollamudi SV, Kushner BH *et al*. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000; **46**(4): 969–74.
17. Gatcombe HG, Marcus RB Jr, Katzenstein HM, Tighiouart M, Esiashvili N. Excellent local control from radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2009; **74**(5): 1549–54.
18. Robbins JR, Krasin MJ, Pai Panandiker AS *et al*. Radiation therapy as part of local control of metastatic neuroblastoma: the St Jude Children's Research Hospital experience. *J Pediatr Surg* 2010; **45**(4): 678–86.
19. Kalapurakal JA, Dome JS, Perlman EJ *et al*. Management of Wilms' tumour: current practice and future goals. *Lancet Oncol* 2004; **5**(1): 37–46.
20. Nicolin G, Taylor R, Baughan C *et al*. Outcome after pulmonary radiotherapy in Wilms' tumor patients with pulmonary metastases at diagnosis: a UK Children's Cancer Study Group, Wilms' Tumour Working Group study. *Int J Radiat Oncol Biol Phys* 2008; **70**(1): 175–80.
21. Terezakis SA, Wharam MD. Radiotherapy for rhabdomyosarcoma: indications and outcome. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 27–35.
22. Mandeville HC. Radiotherapy in the management of childhood rhabdomyosarcoma. *Clin Oncol (R Coll Radiol)* 2019; **31**(7): 462–70.
23. Michalski JM, Meza J, Breneman JC *et al*. Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in Intergroup Rhabdomyosarcoma Study Group trials II through IV. *Int J Radiat Oncol Biol Phys* 2004; **59**(4): 1027–38.
24. Raney RB, Walterhouse DO, Meza JL *et al*. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 protocol, using vincristine and dactinomycin with or without cyclophosphamide and radiation therapy, for newly diagnosed patients with low-risk embryonal rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol* 2011; **29**(10): 1312–8.
25. Lobo S, Gaze MN, Slater O *et al*. Bladder function after conservative surgery and high-dose rate brachytherapy for bladder-prostate rhabdomyosarcoma. *Pediatr Blood Cancer* 2022; **69**(8): e29574.

11
Paediatric cancer

26. Gaze MN, Smeulders N, Ackwerh R *et al*. A national referral service for paediatric brachytherapy: an evolving practice and outcomes over 13 years. *Clin Oncol (R Coll Radiol)* 2023 Apr; **35**(4): 237–244.
27. Cameron AL, Elze MC, Casanova M *et al*. The impact of radiation therapy in children and adolescents with metastatic rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys* 2021; **111**(4): 968–78.
28. Bolling T, Hardes J, Dirksen U. Management of bone tumours in paediatric oncology. *Clin Oncol (R Coll Radiol)* 2013; **25**(1): 19–26.
29. Lopez JL, Cabrera P, Ordonez R *et al*. Role of radiation therapy in the multidisciplinary management of Ewing's sarcoma of bone in pediatric patients: an effective treatment for local control. *Rep Pract Oncol Radiother* 2011; **16**(3): 103–9.
30. Uezono H, Indelicato DJ, Rotondo RL *et al*. Treatment outcomes after proton therapy for Ewing sarcoma of the pelvis. *Int J Radiat Oncol Biol Phys* 2020; **107**(5): 974–81.
31. Andreou D, Ranft A, Gosheger G *et al*. Which factors are associated with local control and survival of patients with localized pelvic Ewing's sarcoma? A retrospective analysis of data from the Euro-EWING99 trial. *Clin Orthop Relat Res* 2020; **478**(2): 290–302.
32. Merchant TE, Kun LE, Wu S, Xiong X, Sanford RA, Boop FA. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. *J Clin Oncol* 2009; **27**(22): 3598–604.
33. Gnekow AK, Kandels D, Tilburg CV *et al*. SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. *Klin Padiatr* 2019; **231**(3): 107–35.
34. CCLG guidelines for the diagnosis and management of paediatric and adolescent low-grade glioma. www.cclg.org.uk/member-area/treatment-guidelines/CNS-radiotherapy (accessed 10 Jan 2023).
35. Karremann M, Gielen GH, Hoffmann M *et al*. Diffuse high-grade gliomas with H3 K27M mutations carry a dismal prognosis independent of tumor location. *Neuro Oncol* 2018; **20**(1): 123–31.
36. Janssens GO, Jansen MH, Lauwers SJ *et al*. Hypofractionation vs conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma: a matched-cohort analysis. *Int J Radiat Oncol Biol Phys* 2013; **85**(2): 315–20.
37. Janssens GO, Gandola L, Bolle S *et al*. Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: a matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group. *Eur J Cancer* 2017; **73**: 38–47.
38. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *Lancet Oncol* 2009; **10**(3): 258–66.
39. Ruda R, Reifenberger G, Frappaz D *et al*. EANO guidelines for the diagnosis and treatment of ependymal tumors. *Neuro Oncol* 2018; **20**(4): 445–56.
40. Bailey S, Andre N, Gandola L, Massimino M, Rutkowski S, Clifford SC. Clinical trials in high-risk medulloblastoma: evolution of the SIOP-Europe HR-MB trial. *Cancers (Basel)* 2022; **14**(2).
41. Mynarek M, Milde T, Padovani L *et al*. SIOP PNET5 MB trial: history and concept of a molecularly stratified clinical trial of risk-adapted therapies for standard-risk medulloblastoma. *Cancers (Basel)* 2021; **13**(23).
42. Packer RJ, Gajjar A, Vezina G *et al*. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol* 2006; **24**(25): 4202–8.
43. Lannering B, Rutkowski S, Doz F *et al*. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. *J Clin Oncol* 2012; **30**(26): 3187–93.
44. Gajjar A, Chintagumpala M, Ashley D *et al*. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol* 2006; **7**(10): 813–20.

11
Paediatric cancer

45. Calaminus G, Kortmann R, Worch J *et al*. SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease. *Neuro Oncol* 2013; **15**(6): 788–96.
46. Fangusaro J, Wu S, MacDonald S *et al*. Phase II trial of response-based radiation therapy for patients with localized CNS nongerminomatous germ cell tumors: a Children's Oncology Group study. *J Clin Oncol* 2019; **37**(34): 3283–90.
47. Murray MJ, Bartels U, Nishikawa R, Fangusaro J, Matsutani M, Nicholson JC. Consensus on the management of intracranial germ-cell tumours. *Lancet Oncol* 2015; **16**(9): e470-e7.
48. www.cclg.org.uk/guidelines/endocrine/craniopharyngioma (accessed 18/4/23).
49. Merchant TE, Kun LE, Hua CH *et al*. Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys* 2013; **85**(4): e187–92.
50. Bishop AJ, Greenfield B, Mahajan A *et al*. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *Int J Radiat Oncol Biol Phys* 2014; **90**(2): 354–61.

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