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COVID-19 Rapid Communication

A rapid review of evidence and recommendations from the SIOPE radiation oncology working group to help mitigate for reduced paediatric radiotherapy capacity during the COVID-19 pandemic or other crises ☆

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ABSTRACT

Objective: To derive evidence-based recommendations for the optimal utilisation of resources during unexpected shortage of radiotherapy capacity.
Methods and materials: We have undertaken a rapid review of published literature on the role of radiotherapy in the multimodality treatment of paediatric cancers governing the European practise of paediatric radiotherapy. The derived data has been discussed with expert paediatric radiation oncologists to derive a hierarchy of recommendations.
Results: The general recommendations to mitigate the potential detriment of an unexpected shortage of radiotherapy facilities include: (1) maintain current standards of care as long as possible (2) refer to another specialist paediatric radiotherapy department with similar level of expertise (3) prioritise use of existing radiotherapy resources to treat patients with tumours where radiotherapy has the most effect on clinical outcome (4) use chemotherapy to defer the start of radiotherapy where timing of radiotherapy is not expected to be detrimental (5) active surveillance for low-grade tumours if appropriate and (6) consider iso-effective hypofractionated radiotherapy regimens only for selected patients with predicted poor prognosis. The effectiveness of radiotherapy and recommendations for prioritisation of its use for common and challenging paediatric tumours are discussed.
Conclusion: This review provides evidence-based treatment recommendations during unexpected shortage of paediatric radiotherapy facilities. It has wider applications for the optimal utilisation of facilities, to improve clinical outcome in low- and middle-income countries, where limited resources continue to be a challenge.

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Table 1
Levels of evidence and grades of recommendation [11].

Level of Evidence		Grades of Recommendation	
Level	*Description*	*Grade*	*Description*
1	Meta-analysis or Systematic reviews of randomised controlled trials (RCT) or RCT with a low risk of bias	A	At least one meta-analysis, systematic review or RCT with a low risk of bias
2	High qualify systematic reviews of cohort studies, high-quality cohort studies or well-conducted cohort studies	B	High qualify systematic reviews of cohort studies, high quality cohort studies or extrapolated from RCT with a low risk of bias
3	Non-analystic studies e.g. institutional series	C	Well-conducted cohort studies or extrapolated from high qualify systematic reviews of cohort studies or high quality cohort studies
4	Expert opinion	D	Level 3 or 4 or extrapolated from well-conducted cohort studies

With the current Covid 19 pandemic, healthcare systems are severely strained [1–3]. So far, infection and severe complications have been less common in children [4]. Nevertheless the pandemic is expected to have an impact on the capacity to deliver paediatric radiotherapy, particularly where general anaesthesia is required, due to shortages of personnel, protective equipment, ventilators and machine time, as well as coping infected children and families [5,6]. Sudden shortage of resources may also occur during other natural disasters and following machine failures, including particle beam facilities [7]. Limited radiotherapy resources are a major obstacle in improving outcomes in low- and middle-income countries where more than two-thirds of paediatric cancers are diagnosed [8].

National guidelines are being issued to provide continuous adult cancer care without increasing the risk of COVID infection [9,10]. Provision of uninterrupted and effective paediatric cancer care faces numerous challenges: most childhood cancers are aggressive, necessitating urgent treatment, most children are treated in international collaborative trials [4] and increasingly paediatric tumours are prioritised for treatment with proton therapy, which may entail travelling some distance.

In an attempt to minimise the potential detriment on clinical outcomes for children with cancer from interruption of radiotherapy services, European paediatric radiation oncology experts have undertaken a rapid review of the role of radiotherapy in the multidisciplinary care of childhood cancers, and considered alternatives for radiotherapy when it is impossible to deliver the internationally acceptable standard of care. This guideline attempts to standardise approaches to paediatric radiotherapy in times of intense resource constraints to deliver safe, high quality treatment.

Methods

Experts from the European Society of Paediatric Oncology (SIOPE) Radiation Oncology Working Group have developed rapid evidence-based recommendations for effective clinical practise with minimal variation by asking:

1. For which paediatric tumours are radiotherapy and its timing important in optimising chances of cure?
2. Can we safely defer radiotherapy for any tumour types and if so, with what acceptable delay?
3. Can chemotherapy be used to delay radiotherapy if it is still available and deemed appropriate.
4. If resources are constrained, can hypofractionated regimens be used for any paediatric tumours?
5. When are radiotherapy dose corrections needed during unforeseen treatment interruptions?
6. Can radiotherapy be used as a neoadjuvant ‘bridging’ treatment when primary surgery or systemic treatment is not available?

Four authors (GOJ, HCM, TA, TVB) independently reviewed published literature from European centres, including prospective randomised clinical trials, to evaluate the levels of evidence [11] (Table 1). The synthesised data has been discussed with expert paediatric radiation oncologists, including principal investigators of ongoing SIOPE trials.

Results and recommendations

General measures to mitigate detrimental clinical effects in an unexpected shortage of radiotherapy facilities

- Current standard treatments, whether in trials or using approved guidelines, should be maintained if possible. Consider suspension of trials if the additional resources needed to run them become unavailable.
- Consider referral to another specialist paediatric radiotherapy department.
- Prioritise using existing radiotherapy resources to treat patients with tumours where radiotherapy has a high impact on outcome.
- Standard or maintenance chemotherapy can be used to defer radiotherapy in chemo-sensitive tumours where this delay is not expected to be detrimental (e.g. rhabdomyosarcoma and Ewing sarcoma, medulloblastoma, ependymoma, and germ cell tumours presenting with metastases.)
- Consider active surveillance (for WHO grade I–II primary central nervous system low-grade gliomas and craniopharyngiomas after initial biopsy or debulking surgery).
- Consider isoeffective hypofractionated radiotherapy schedules (which also reduce overall treatment time), changing dose per fraction from 1.6–1.8 Gy to above 2.0 Gy, for selected poor prognosis patients where radiotherapy cannot be safely deferred, (neuroblastoma, rhabdomyosarcoma, Ewing sarcoma and high-grade or diffuse midline gliomas).
- For highly proliferative tumours (rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, germ cell tumours, and atypical teratoid rhabdoid tumours [ATRT}), treatment gap corrections should be applied if the planned duration of treatment is extended by >1 week.
- Omit radiotherapy in patients with poor prognostic tumours and or who need palliative care if symptom can be controlled by other measures [12,13].
- Any deviation from standard of care radiotherapy should be agreed in multi-disciplinary team (MDT) meetings.

Level of evidence and recommendations for common paediatric malignancies

The following section provides a summary of evidence for the effectiveness of radiotherapy and recommendations for treatment of common and challenging paediatric tumours:

Neuroblastoma

- *Evidence*
  - 1.5 Gy has been the standard dose per fraction in SIOPEN trials so far, but German and US schedules use 1.8 Gy per fraction [14,15] and will be the dose per fraction in the next SIOPEN high risk protocol (level 2)
  - Hypofractionation has been used for palliation in paediatric tumours including neuroblastoma, with effective disease control and a favourable side effect profile [16] (level 3).
  - In high risk neuroblastoma, immunotherapy after radiotherapy increases survival [17] (level 2)
- *Recommendation*
  - Standard treatment should be given wherever possible (grade B)
  - 1.8 Gy per fraction can now be considered as standard (grade B)
  - 3 Gy per fraction can be used in case of significantly reduced capacity (grade C)
  - In high risk neuroblastoma, and if capacity is severely reduced, immunotherapy can be given before radiotherapy (grade D)
  - In intermediate risk neuroblastoma treatment can be delayed up to 4 weeks (grade D)

Wilms' tumour

- *Evidence*
  - A fraction dose of 1.8 Gy with reduction to 1.5 Gy is recommended for irradiation of the flank and whole abdomen/lung, respectively, and is the standard in the SIOP-RTSG UMBRELLA 2016 protocol [18] (level 2).
  - Simultaneous integrated boost (SIB) techniques can be considered for patients with residual lung metastases at the time of radiotherapy [18] (level 2).
  - After pre-operative chemotherapy and surgery, adjuvant radiotherapy is started within 1–2 weeks from onset of adjuvant chemotherapy, unless metastatic disease is present [19] (level 2).
  - In stage IV disease with potential indication for radiotherapy to the lungs and flank/abdomen, abdominal radiotherapy can be postponed up to week 10 to avoid a gap or overlap If the recurrence rate is estimated to be high, abdominal +/− lung [depending on response] radiotherapy may be given earlier [20] (level 2).
- *Recommendation*
  - Standard treatment should be given wherever feasible (grade B).
  - 1.8 Gy or 1.5 Gy per fraction, depending on the volume, remains the standard (grade B).
  - In patients with intermediate-risk and high-risk disease without distant metastases, deferral of flank or whole abdomen irradiation can be discussed within the UMBRELLA panel (grade D).

Paediatric soft tissue sarcoma

- *Evidence*
  - 1.8 Gy per fraction is recommended by the major international collaborative groups, including EpSSG, COG and CWS, and is the standard in the new EpSSG FaR-RMS study [15,21] [level 2]. Two Gy per fraction has been used for TYA patients, particularly in NRSTS, mirroring adult soft tissue sarcoma (STS) schedules.
  - Simultaneous integrated boost (SIB) techniques can be considered, with increased dose per fraction up to 2.2–2.3 Gy; SIB schedules are incorporated into the FaR-RMS radiotherapy guidelines. For localised disease, standard of care definitive radiotherapy should start between week 12 and week 16; for metastatic disease RT is given with cycle 8 of chemotherapy (week 22); Detrimental outcomes have been observed when radiotherapy is delayed beyond week 24 [15,22] [level 2].
  - Routine use of radiotherapy, either adjuvant or definitive, for high risk rhabdomyosarcoma was a key factor in improvement in EFS and OS in EpSSG RMS 2005 [21] [level 2]
  - Post-operative radiotherapy (PO-RT) can be deferred for RMS until the 4th cycle of post op chemotherapy (week 24) (FaR-RMS).
  - For NRSTS, PO-RT may be used preferentially instead of pre-operative RT where there are capacity issues, and although recommended within 3 weeks of surgery can be deferred for up to 6 weeks, (COG ARST 1321 NRSTS study guideline).
  - In metastatic NRSTS, radiotherapy can be deferred to the 8th cycle of chemotherapy (week 22–25) (BERNIE study [23].
  - Hypofractionation ($\geq$3Gy/f) has been used to treat metastatic STS, achieving high levels of local control [24].
  - Hypofractionated stereotactic body radiotherapy for spinal/paraspinal metastases is being used in current French SBRT study: 27 Gy in 3 fractions or 35 Gy in 5 fractions.
- *Recommendation*
  - Standard treatment should be given wherever feasible (grade B)
  - 1.8 Gy per fraction remains the standard (grade B)
  - If capacity if reduced
    - Consider deferral of radiotherapy (grade C).
    - Consider omitting radiotherapy for standard risk RMS achieving complete response; this strategy has inferior EFS but not OS [12] [level2, grade C].
    - 3 Gy per fraction can be used, or even SBRT (grade D).

Ewing sarcoma

- *Evidence*
  - 1.8 Gy per fraction is recommended, including in the recent EURO EWING 2012 and COG studies. 2.0 Gy per fraction has been used for TYA or adult patients, mirroring adult sarcoma RT schedules (level 2).
  - Hypofractionation ($\geq$3 Gy/f) has been used to treat metastatic STS and ES, achieving high levels of local control [24] (level 3).
  - SBRT has demonstrated good local control in small single centre series [25]; it is being evaluated in the French SBRT study (see above), and the COG AEWS1221 Ewing study where 30–40 Gy in 5 fractions is being used for bone metastases (level 3).
- *Recommendation*
  - Standard treatment (1.8 Gy per fraction) should be given wherever feasible (grade B).
  - Simultaneous integrated boost (SIB) techniques can be considered, with increased dose per fraction up to 2.2–2.3 Gy. Consider deferral of radiotherapy if reduced capacity (grade C).
  - If capacity is reduced, 3 Gy per fraction can be used, or even SBRT (grade D).

Hodgkin lymphoma

- *Evidence*
  - Most protocols for the treatment of paediatric Hodgkin lymphoma have used 1.5–1.8 Gy fractions [26–28]. However, in adult Hodgkin lymphoma, 2 Gy fractions are standard [29]. In addition, the boost dose per fraction is also 2 Gy in the EuroNet protocol (level 2).

- There are convincing data on detriment from delaying radiotherapy after chemotherapy [30] and according to the EuroNet protocol treatment should start within 3–6 weeks after chemotherapy (level 2).

- *Recommendation*
  - Standard treatment should be given wherever possible (grade B)
  - 2 Gy per fraction can be used instead of 1.5–1.8 Gy (grade C)

Leukaemia

- *Evidence*
  - Although in some countries TBI is given in 8 fractions twice daily, the current standard is 12 Gy in 6 fractions twice daily [31] (level 2).
  - For total body irradiation (TBI) in adult patients, single-dose daily fractionation has proven to be non-inferior to twice-a-day fractionated TBI before allogeneic stem cell transplantation for acute leukaemia [32] (level 2).
  - For TBI, single or 2 fraction treatments have been used instead of 6 fraction treatments; however at cost of increased toxicity and inferior results [33] (level 3). Replacing TBI by chemotherapy (fludarabine, thiotepa, busulfan and treosulfan) regimens can also be considered, but is associated with inferior results in acute lymphoblastic leukaemia (interim analysis of ALL SCTPed 2012 FORUM trial).
  - For paediatric leukemic CNS relapse, radiotherapy in 1.5–1.8 Gy fractions is often used in addition to chemotherapy [34], while in adults 2 Gy fractions are more common (level 2).
  - For paediatric leukemic testicular relapse, 1.5–1.8 Gy fractions are commonly used after orchidectomy while 2 Gy fractions are used if no orchidectomy has been performed [35] (level 2).
- *Recommendation*
  - Standard treatment should be given wherever possible (grade B)
  - If capacity is reduced
    - 12 Gy fractionated TBI can be delivered safely in terms of disease control and survival with a single daily dose of 3 or 4 Gy/d instead of 6 fractions of 2 Gy BID. (grade B)
    - Replacing TBI by chemotherapy only conditioning regimens can be considered, but is associated with inferior results in ALL (grade C). In case of severely reduced capacity, single (7.5–8 Gy) or two fraction (2 × 4.5 Gy) TBI can be used at the expense of increased toxicity and slightly inferior results (grade D)
  - For paediatric leukemic CNS relapse, dose per fraction can be increased to 2 Gy. Alternatively, an additional course of chemotherapy can be given (grade C)
  - For paediatric leukemic testicular relapse, dose per fraction can be increased to 2 Gy. Alternatively, an additional course of chemotherapy can be given (grade C)

Medulloblastoma

- *Evidence*
  - In non-infant children and TYA with medulloblastoma, postoperative craniospinal radiotherapy with boost gives best survival [36–39] (Level I)
  - Delay in starting radiotherapy beyond 49 days after surgery significantly reduces 5-year EFS [40] (Level II)
  - For infant medulloblastoma, chemotherapy is generally adopted to delay or avoid the need for radiotherapy [41,42] (Level I)
  - Hypofractionated radiotherapy has not been studied in standard adjuvant treatment for medulloblastoma. Hypofractionated regimens provide effective palliation in a select group of patients considered for reirradiation [43,44] (Level III)
  - Radiotherapy should start ideally at 28–40 days after surgery. Delay beyond 40 days should be avoided (level III)
- *Recommendation*
  - Standard postoperative radiotherapy should be given to all non-infant children and TYA after initial surgery (Grade A).
  - Hypofractionated radiotherapy is not recommended for standard adjuvant treatment (grade B)
  - For infant medulloblastoma, chemotherapy with delayed or no radiotherapy is recommended (grade B)

Ependymoma

- *Evidence*
  - Postoperative radiotherapy (59.4 Gy in 33 fractions) improves clinical outcome with acceptable toxicity even in children younger than 3 years (17–21). A dose modification to 54 Gy in 30 fractions is recommended in very young children (<12 months) or those undergoing multiple surgeries for tumours near the brainstem because of possible increased risk of brainstem toxicity in these patient groups [45–48] (Level I).
  - Radiotherapy should ideally start within 6 weeks of surgery (Level III)
  - There is no proven role for the use of chemotherapy to delay radiotherapy. However, chemotherapy is used in children ≤12 months to delay radiotherapy [49,50] (Level II).
  - There are no studies of hypofractionated adjuvant radiotherapy for ependymoma.
- *Recommendation*
  - All patients except children ≤12 months with ependymoma should receive postoperative radiotherapy at the standard dose/fractionation of 59.4 Gy in 33 daily fractions (Grade A)
  - Radiotherapy should start within 6 weeks of surgery (Grade C)
  - Use of chemotherapy as bridging strategy is not recommended, except for children less than ≤12 months of age (Grade A)

High grade glioma including diffuse midline glioma (DMG) of pontine, and non-pontine origin

- *Evidence*
  - 30 fractions of 1.8 Gy are most commonly given for all HGG, including DMG [51–53] (level 2).
  - Hypo-fractionation using 13 fractions of 3.0 Gy results in comparable overall survival rates in patients with DMG of pontine origin [51,53] (level 1**)**
  - The utility of systemic agents for newly diagnosed DMG of pontine origin remains unproven [54] (level 2**)**
  - A slightly improved outcome is observed in children who received lomustine in addition to temozolomide for subtotally-resected glioblastoma with MGMT overexpression [55] (level 2)
  - In adults with glioblastoma, delays >8 weeks in patients with GTR resulted in worse survival [56] (level 1)
- *Recommendation*
  - Hypo-fractionation using 3.0 Gy is an alternative to normofractionation to lower the treatment burden in patients with DMG of pontine origin [grade B], and for patients with HGG from non-pontine origin and unfavourable molecular profile (grade D).

- For primary treatment, the biologic behaviour of the tumour determines time of starting radiotherapy. In most patients it is limited from days to a couple of weeks (grade D).
- For GTR/NTR after surgery, radiotherapy should start within 4–8 weeks (grade B).

Low-grade glioma

- *Evidence*
  - Fractionation using 1.8 Gy is generally accepted as standard of care [57–59]. A dose of 50.4–54 Gy is most recommended (Level II)
  - There is some evidence for better tumour control with 54 Gy [60] (Level III)
  - Optimal timing of radiotherapy is not known [61] (level III).
- *Recommendation*
  - Standard treatment (50.4–54 Gy using 1.8 Gy per fraction) should be given whenever possible (Grade B)
  - In case of reduced capacity, in absence of symptoms or systemic options, delay treatment until next MRI-scan (Grade B)
  - 50–54 Gy using 2 Gy per fraction could be considered (grade D)

Intracranial germ cell tumours

- *Evidence*

Intracranial germinoma

- In localised disease, primary chemotherapy followed by a total dose of 40 Gy [62] in 1.6 Gy fractions is standard for this highly radiosensitive tumour (level 2).
- Although chemo-sensitive, germinoma is not chemo-curable and radiotherapy has a major role in local control and cannot be omitted [63,64] (level 2)
- In localised germinoma, ventricular irradiation to reduce regional subependymal relapse necessitates 24 Gy at 1.6 Gy per fraction [65], followed by tumour bed boost (level 2)
- In disseminated germinoma, CSI irradiation 1.6 Gy per fraction/TD 24 Gy followed by boost 1.6 Gy/TD 16 Gy is associated with a high level of disease control [62] (level 2)

Non-germinoma GCT

- Primary chemotherapy with surgery for operable residue and radiotherapy is the standard of care to improve local control in all cases.
- For localised disease: Focal RT, 1.8 Gy per fraction up to 54 Gy remains the recommendation in Europe [62] (level 2).
- For metastatic disease: craniospinal irradiation 1.5 Gy per fraction to 30 Gy followed, by boost to 54 Gy [62] (level 2)

- *Recommendation*

Germinoma

- Standard treatment should be given whenever possible (Grade B)
- Post chemotherapy boost dose per fraction to tumour bed may be safely increased to 1.8–2 Gy if needed (grade D).
- Hypofractionation is inappropriate (grade A)
- Delay of post chemotherapy RT should be limited (1–2 weeks) (grade B)
- For disseminated germinoma, pre-RT chemotherapy may be safely used for up to 4 cycles to delay craniospinal irradiation (grade C).

Non-germinoma GCT

- For localised disease, 1.8 Gy per fraction up to 54 Gy should be used preferentially, but 2 Gy per fraction may be considered especially if target volume is small (grade D).
- For metastatic disease, 1.8 Gy craniospinal and 1.8–2 Gy boost fractions may be applied (grade D)

Atypical Teratoid/Rhabdoid Tumours (ATRT)

- *Evidence*
  - Standards and evidence about RT in ATRT are sparse.
  - Within the German HIT trial, patients were treated with 1.6 Gy fractions for CSI volume and 1.8 Gy fractions for local fields (level 2)
  - The European EURHAB protocol used 1.6 Gy fractions for CSI and 1.8 Gy for tumour bed, r [66]; children treated were extremely young (level 2)
  - St. Jude's approach uses 1.8 Gy fractions for CSI and local fields [67] (level 3).
  - For the current draft of the future SIOP-ATRT trial, European radiation oncology experts have agreed to use 1.8 Gy fractions for both CSI and local fields [68] (level 4).
  - Chemotherapy is used in many protocols to postpone the start of RT because of very young patient age (level 3).
- *Recommendation*
  - 1.8. Gy fractions can be considered for moderate acceleration of the treatment course during CSI phase (grade C).
  - 2.0 Gy fractions to the local field can be considered for moderate acceleration (grade D).
  - Hypofractionation cannot be recommended due to the extremely young age of the patient except for palliative treatment (grade D).
  - SIB concepts are not appropriate for CSI plus local treatment as the gap between CSI and local dose is too large to avoid high doses per fraction (grade D).
  - After interdisciplinary discussion chemotherapy may be used for good responders without evidence of disease to delay onset of RT (grade D).

Conclusions

Existing evidence for the clinical practise of paediatric radiotherapy and details of ongoing SIOPE clinical trials are used here to derive an evidence-based treatment recommendation during unexpected shortage of radiotherapy facilities. This guideline may have a wider application in optimising the use of paediatric radiotherapy to improve clinical outcome in low- and middle-income countries, where limited resources continue to be a challenge. This article also highlights the important radiotherapy questions which need to be addressed in future clinical trials.

This rapid review and recommendation will serve only as a guide to MDTs and are not meant to replace the important network

of national and international paediatric radiotherapy experts that regularly give advice. We wish to highlight the importance of recording outcomes for children who receive radical radiotherapy where there have been modifications in fractionation or timing of treatment due to unexpected shortage of facilities such as during the COVID-19 epidemic so that there can be shared learning in the future.

Conflict of interest statements

There are no conflicts of interest to declare.

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