Clinical Oncology 31 (2019) 182–190

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

The Evidence for External Beam Radiotherapy in High-Risk Neuroblastoma of Childhood: A Systematic Review

S. Arumugam *, N.J. Manning-Cork *, J.E. Gains *, T. Boterberg †, M.N. Gaze *

* Department of Oncology, University College London Hospitals NHS Foundation Trust, London, UK
† Department of Radiation Oncology, Ghent University Hospital, Gent, Belgium

Received 5 October 2018; accepted 27 October 2018

Abstract

Aims: External beam radiotherapy is widely used in various ways in the management of neuroblastoma. Despite extensive clinical experience, the precise role of radiotherapy in neuroblastoma remains unclear. The purpose of this systematic review was to survey the published literature to identify, without bias, the evidence for the clinical effectiveness of external beam radiotherapy as part of the initial multimodality treatment of high-risk neuroblastoma. We considered four areas: treatment of the tumour bed and residual primary tumour, identification of any dose–response relationship, treatment of metastatic sites, identification of any technical advances that may be beneficial. We also aimed to define uncertainties, which may be clarified in future clinical trials.
Materials and methods: Bibliographic databases were searched for neuroblastoma and radiotherapy. Reviewers assessed 1283 papers for inclusion by title and abstract, with consensus achieved through discussion. Data extraction on 57 included papers was carried out by one reviewer and checked by another. Studies were assessed for their level of evidence and risk of bias, and a descriptive analysis of data was carried out.
Results: Fifteen papers provided some evidence that radiotherapy to the tumour bed and residual tumour may possibly be of value. However, there is a significant risk of bias and no evidence that all subgroups will benefit. There is some suggestion from six papers that dose may be important, but no hard evidence. It remains unclear whether irradiation of metastatic sites is helpful. Technical advances may be of value in radiotherapy of high-risk neuroblastoma.
Conclusions: There are data that show that radiotherapy is of some efficacy in the management of high-risk neuroblastoma, but there is no level one evidence that shows that it is being used in the best possible way. Prospective randomised trials are necessary to provide more evidence to guide development of optimal radiotherapy treatment schedules.

Key words: High-risk; neuroblastoma; radiation; radiotherapy; systematic review

Introduction

Neuroblastoma is a cancer of the sympathetic nervous system that predominantly affects children. The primary tumour most commonly arises from the adrenal medulla or from sympathetic ganglia in other locations. Widespread metastatic disease is often present. The prognosis varies widely, depending on the age of the child, the extent of the disease at diagnosis and various molecular pathology features, especially amplification of the *MYCN* oncogene.

Over the decades, an increasing understanding of the disease has developed, largely as a result of international clinical trials groups' activities. Pooling of data has allowed the International Neuroblastoma Risk Group (INRG) Task Force to refine the staging system and the risk grouping based on large patient numbers. The INRG staging system [1] recognises four stages (see Table 1). The INRG classification system [2] defines very low-, low-, intermediate- and high-risk groups. The high-risk group includes all patients aged over 18 months with stage M disease and patients with stage L1, L2 or MS neuroblastoma and *MYCN* amplification. Although the prognosis of patients with high-risk neuroblastoma is poor, with fewer than half of these patients becoming long-term survivors, it is possible to subdivide this group on the basis of disease characteristics at presentation, defining an ultra-high-risk population with

Address for correspondence: M.N. Gaze, University College London Hospitals NHS Foundation Trust, First Floor Central, 250 Euston Road, London NW1 2PG, UK.
E-mail address: mgaze@nhs.net (M.N. Gaze).

https://doi.org/10.1016/j.clon.2018.11.031
0936-6555/

Table 1
The International Neuroblastoma Risk Group (INRG) staging system

INRG stage	Definition
L1	Localised disease, without imaging-defined risk factors (e.g. encasement of major blood vessels or encroachment into the spinal canal).
L2	Localised disease with imaging-defined risk factors.
M	Metastatic disease that does not fall into the MS category (e.g. those aged less than 18 months with bone metastases, and all older patients with distant metastases).
MS	Age less than 18 months with metastatic disease limited to liver, skin or bone marrow.

an event-free survival probability of less than 10% at 5 years [3].

This paper focuses on radiotherapy for high-risk neuroblastoma. For more general aspects, the reader is referred to other reviews [4,5].

Although treatment protocols vary between clinical trials groups, in general treatment for high-risk neuroblastoma is similar worldwide. Long intensive schedules are used, integrating systemic and local treatments. Induction chemotherapy aims to eradicate or at least reduce metastatic disease and downstage the primary tumour prior to surgery. Consolidation by high-dose chemotherapy follows, and then radiotherapy to the tumour bed. Minimal residual disease therapy including differentiating agents and immunotherapy completes the treatment.

There is strong evidence from randomised trials for many of the systemic therapies. For example, the value of high-dose, myeloablative chemotherapy consolidation has been shown in comparison with no high-dose chemotherapy in three randomised trials [6–8] and the superiority of one high-dose regimen over another in a fourth [9]. Although surgery and radiotherapy are recommended in almost all current high-risk neuroblastoma treatment strategies, there is much less evidence to support their use.

This paper reports a systematic review of the evidence for the value of external beam radiotherapy as part of the initial multimodality management of high-risk neuroblastoma. Although radiotherapy is also used in selected patients with intermediate-risk neuroblastoma, its use in this situation is not specifically explored here. Intraoperative radiotherapy during surgery for high-risk neuroblastoma has been investigated in some centres, but not generally adopted, so is not covered. Historically, total body irradiation (TBI) was used with high-dose chemotherapy and bone marrow rescue as part of some consolidation schedules, but has fallen out of favour as the long-term side-effects of this approach have become apparent, and as evidence for the effectiveness of a chemotherapy-alone consolidation strategy has accrued. The role of TBI is not evaluated here, although some papers reporting its use form part of the evidence for radiotherapy in general. Molecular radiotherapy is widely used in neuroblastoma. Most commonly this utilises iodine-131 meta-iodobenzylguanidine (mIBG), but other radiopharmaceuticals, for example lutetium-177 DOTATATE have also been evaluated [10]. As we have previously carried out a systematic review of mIBG therapy [11], we do not revisit molecular radiotherapy. Palliative radiotherapy can be useful in progressive or relapsed disease [12], but does not form part of this review.

The aims of this review were to answer four questions about the value of external beam radiotherapy as part of initial treatment schedules for high-risk neuroblastoma in childhood.

- Does radiotherapy to the primary tumour bed or residual tumour confer benefit?
- Is there evidence for a dose–response relationship?
- Is there evidence to support the use of radiotherapy to metastatic sites as well as to the tumour bed?
- What is the evidence that technical advances in radiotherapy may be of value?

Materials and Methods

Typical systematic review methods were used according to a plan defined at the outset. Bibliographic and clinical trial databases (MEDLINE via PubMed and the Cochrane Library) were searched for English-language articles from inception to August 2018. The search terms were 'radiotherapy' OR 'radiation' AND 'neuroblastoma'. Two reviewers independently examined the titles and abstracts of the search results, with differences resolved by consensus. The purpose was to discard articles clearly of no relevance and to identify those that might contain useful data. The full text of each of these papers was then obtained and evaluated. Papers with no information relevant to the four questions were discarded. Data from informative studies were extracted by one reviewer and checked by another.

The Oxford Centre for Evidence-based Medicine (CEBM) – Levels of Evidence system was used to grade results [13]. The risk of bias in a randomised study was explored using the Cochrane Risk of Bias tool [14] and in non-randomised studies where appropriate by the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool [15]. In the absence of good quantitative data, the findings have been summarised qualitatively using the PICO system, where P represents patient, problem or population, I relates to the intervention, C is the comparison, control or comparator, and O is the outcome measure [16]. Finally, we used the GRADE system (Grading of Recommendations, Assessment, Development and Evaluations) to assess the evidence collectively for each question [17].

Results

The MEDLINE search via PubMed was last updated on 17 August 2018. In total, 1283 items were returned. It was decided only to include those since 1978; earlier

publications were discarded as most were title only without abstracts. In addition, so much has changed in neuroblastoma diagnosis and treatment, that publications from more than 40 years ago, reporting patients treated more than 50 or 60 years ago, would be most unlikely to have valuable information. These patients would have been: staged without the use of magnetic resonance or computed tomography imaging, mIBG scintigraphy and positron emission tomography scanning; risk stratified without any molecular pathology information; and treated with obsolete radiotherapy techniques; treated without modern chemotherapy and immunotherapy schedules. This date restriction removed 62 items. The Cochrane Library search identified two systematic reviews and 71 trial reports, none of which were additional to those selected from MEDLINE.

Of the 1221 titles and abstracts reviewed, 1164 were excluded, leaving just 57 papers for full scrutiny. See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Figure 1 for details of exclusions.

Does Radiotherapy to the Primary Tumour Bed or Residual Tumour Confer Benefit?

The abstract and title review yielded 32 publications, which might help to answer whether radiotherapy to the primary tumour site might confer benefit, or give information about a dose–response relationship. After scrutiny of the full papers, eight were excluded as being of no value.

Radiotherapy has a long history in all risk groups of neuroblastoma, indicating a perceived value. The proportion of patients receiving radiotherapy has declined over decades, from 60% in the 1970s to 25% in the 2000s, probably because of a better understanding of which risk groups it will not benefit [18]. Population-based studies do not provide evidence for the benefit of radiotherapy [19,20]. The aim of radiotherapy is to provide local control. Although most patients with high-risk neuroblastoma die from uncontrolled metastatic disease, there is evidence that improved local control predicts better overall survival [21].

Only one randomised trial of radiotherapy in neuroblastoma has been carried out [22]. The population comprised only patients greater than 1 year old at diagnosis with Pediatric Oncology Group stage C neuroblastoma, broadly equivalent to INRG stage L2 disease. Most of these patients would today be classified as intermediate risk, but a minority are likely to have had *MYCN* amplification and so would now be classed as high risk. After primary surgery, the experimental intervention was radiotherapy to the tumour bed and any residual tumour present, with lower dose 'prophylactic' radiotherapy to the uninvolved thoracic paravertebral and supraclavicular lymph nodes. The control population received no radiotherapy. All patients received the same chemotherapy. Radiotherapy was allocated to 33, and no radiotherapy to 29, eligible patients. The event-free survival and overall survival rates were 59% and 73% for those receiving radiotherapy and 32% and 41% for those not receiving radiotherapy ($P = 0.009$ event-free survival; $P = 0.008$ overall survival). One cannot extrapolate the conclusion that radiotherapy is beneficial in this specific group of patients to the wider high-risk neuroblastoma population. Although a benefit from radiotherapy was observed in this population, it might not have been the case if contemporary chemotherapy and surgical practices had been used in both arms.

One randomised trial in which radiotherapy was not the primary question but was used consistently in the form of TBI in one randomised arm, together with selective use of

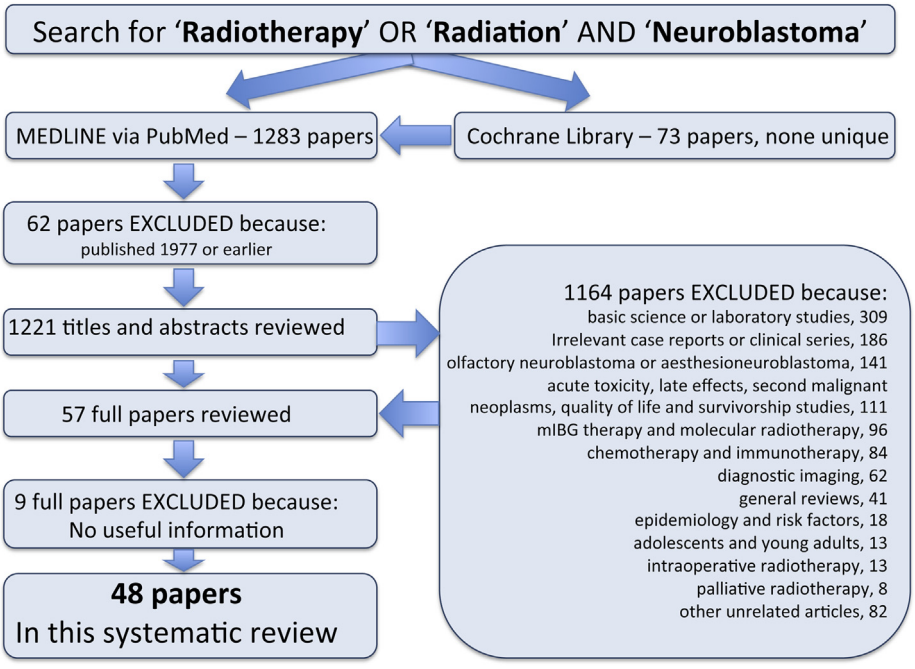

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) diagram for papers reviewed.

boost irradiation of the tumour bed in both arms, provides good evidence for radiotherapy [23,24]. The population comprised 593 high-risk neuroblastoma patients who were randomised to a TBI containing high-dose chemotherapy myeloablative regimen or continuing conventional dose chemotherapy. In both arms, 10 Gy external beam radiotherapy was given selectively to those with residual disease at the primary site. The local recurrence rate was 33% in the TBI arm versus 51% in the continuing chemotherapy arm. In those who received TBI and a boost, the local recurrence rate was only 22%.

In Germany, the national philosophy has been to avoid radiotherapy in patients after a complete resection and to give 36 Gy to patients with residual primary tumours [25]. Among 110 high-risk patients, 13 with irradiated residual masses had an event-free survival of 85%, 23 with residual masses and no radiotherapy had an event-free survival of only 25%. Seventy-four without residual masses and no radiotherapy had an event-free survival of 61%. This suggests that the use of radiotherapy results in a significant improvement in patients with residual disease; it does not answer the question about those where resection has been complete.

Similarly, in a single-institution series where radiotherapy was given to some but not all patients with residual disease, outcomes in both irradiated and unirradiated groups were similar, indicating that radiotherapy might simply compensate for incomplete surgery [26].

In France, outcomes for localised high-risk disease improved significantly following a national change in treatment policy with the introduction of high-dose chemotherapy and radiotherapy for all, rather than just selected, patients with MYCN amplified stage II and III neuroblastoma [27]. In the earlier cohort of 20 patients, the overall survival was 20%, with seven irradiated patients faring as badly as 13 unirradiated. In the second cohort, the event-free survival was 83%. Although this difference is dramatic, it is hard to attribute the benefit to radiotherapy.

A single-institution study showed an improvement in progression-free survival from 22 to 36% in two consecutive cohorts where radiotherapy was introduced [28].

A number of studies have reported good local control in series where radiotherapy has been used as standard [29–36]. These have variably been interpreted as suggesting that radiotherapy is an essential component of treatment or may be reduced. It is hard to tell the true value of radiotherapy from these reports as there are no comparator groups.

See Table 2 for the grading of each paper. When all patients are taken into account, we apply a GRADE certainty rating of moderate: the true effect is probably close to the estimated effect. When subgroups are considered, the GRADE certainty falls to low: the true effect might be markedly different from the estimated effect.

Is There Evidence for a Dose–Response Relationship?

There have been no direct dose comparisons. Various doses from about 21 Gy to about 40 Gy have been used. An attempted dose–response analysis in a series of 76 patients, of whom 33 were infants and only 21 stage IV, where doses were dependent on age, found that the younger patients who received lower doses fared better [37]. The powerful effects of age and stage on prognosis probably obscured any effect of radiotherapy dose. Another descriptive older study using various doses showed age and stage as strong prognostic factors, making conclusions about the effect of dose impossible [38].

Some evidence for a higher dose being more effective comes from studies where TBI was given with an additional tumour bed boost to some patients [24,39]. However, another group following a similar practice found no

Table 2
Does radiotherapy to the primary tumour bed or residual tumour confer benefit? Assessment of the quality of the evidence. GRADE certainty moderate overall, low for subgroups

Reference	CEBM 2011	ROBINS-I	Cochrane risk of bias
Castleberry *et al.* [22]	Step 2		High risk of bias
Matthay *et al.* [23]	Step 2	Low risk of bias	
Haas Kogan *et al.* [24]	Step 2	Low risk of bias	
Simon *et al.* [25]	Step 3	Moderate risk of bias	
Laprie *et al.* [27]	Step 3	Moderate risk of bias	
Robbins *et al.* [26]	Step 4	Serious risk of bias	
De Ioris *et al.* [28]	Step 4	Serious risk of bias	
Wolden *et al.* [29]	Step 4	Serious risk of bias	
Kushner *et al.* [30]	Step 4	Serious risk of bias	
Bradfield *et al.* [31]	Step 4	Serious risk of bias	
Marcus *et al.* [32]	Step 4	Serious risk of bias	
Gatcombe *et al.* [33]	Step 4	Serious risk of bias	
Modak *et al.* [34]	Step 4	Serious risk of bias	
Casey *et al.* [35]	Step 4	Serious risk of bias	
Ferris *et al.* [36]	Step 4	Serious risk of bias	

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; CEBM, Centre for Evidence-based Medicine; ROBINS-I, Risk of Bias in Non-randomised Studies – of Interventions.

difference between those receiving and those not receiving a boost [40].

One small series where patients with residual disease were treated with a range of doses reported a local failure rate of 30% at doses lower than 30 Gy, but zero at higher doses [41].

See Table 3 for the grading of each paper. We assign a GRADE certainty of low: the true effect might be markedly different from the estimated effect.

Is There Evidence to Support the Use of Radiotherapy to Metastatic Sites as Well as to the Tumour Bed as Part of Primary Treatment?

Nine publications were identified that addressed the role of radiotherapy to metastatic sites. One on relapsed disease was excluded.

The largest study [42] described 159 patients with 244 irradiated metastatic sites treated with a median dose of 21 Gy. There was no comparator population. Metastatic control was better in those treated sites that were mIBG negative, following chemotherapy, than in those that remained visible on mIBG scans. It is hard to draw any conclusions about the value of radiotherapy from this study, but the finding that outcomes are worse in the presence of persistent mIBG-positive sites is consistent with other studies.

One study reported 74 relapsed patients by whether or not they had received TBI as part of their initial treatment [43]. Relapse in more than one previously mIBG-positive site occurred in 12 of 23 patients (52%) who had received TBI compared with 40 of 51 (78%) patients who had not received TBI. The main risk of bias is that patients treated in the same way who did not relapse were not studied.

A single-centre study of systematically irradiated metastatic sites with no comparator series showed that survival worsened as the number of treated sites increased [44]. This study provides no evidence that radiotherapy helped, but again the findings are consistent with other data in showing that patients with more disease have worse outcomes.

A single-institution study in which some received radiotherapy to metastatic sites and others did not found no difference on relapse-free or overall survival [45]. This provides no evidence to support the routine use of metastatic radiotherapy.

A multicentre study of 159 mIBG-positive metastatic sites at first relapse showed that 82% of relapses occurred in previous sites of disease [46]. The recurrence rate was higher at 25% in previously unirradiated sites than the 16% observed in irradiated sites. This study is biased by the fact that those patients who did not relapse were not included.

Although metastases may occur in almost any bone, those that occur in the skull can be particularly problematic. A mixed photon and electron technique for irradiating the calvarium and skull base while sparing the brain parenchyma has been described [47]. A subsequent publication detailing outcomes showed that cranial disease was controlled in 79% who had a complete response to initial chemotherapy, but in only 52% with primary refractory disease [48]. There was no comparator population.

A smaller study [49] evaluated patterns of failure in 20 patients where only residual mIBG-positive sites of disease had been treated. There was no comparator population. It was concluded that as relapses occurred in both irradiated and unirradiated sites, further study was warranted.

All of these studies are rated at CEBM step 4, ROBINS-I: serious risk of bias. We attribute these papers a GRADE certainty rating of low: the true effect might be markedly different from the estimated effect.

What is the Evidence that Technical Advances in Radiotherapy May be of Value?

Radiotherapy is continually going through a process of evolution. Newer, more sophisticated techniques may possibly be better than previous versions, but a prospective evaluation of merit is uncommon in a rare disease like neuroblastoma. Here we present a qualitative evaluation of largely theoretical papers and modelling studies or very small case series, rather than clinical trials. The advances reported specifically in relation to neuroblastoma evaluated here are: functional imaging in target volume definition; organ motion control; intensity-modulated radiotherapy; image-guided radiotherapy; proton beam radiotherapy; and radiotherapy quality assurance. Clearly in all these areas there is a huge literature, but our search identified only 16 papers where the technique was specifically applied to neuroblastoma.

Many nuclear medicine techniques for functional imaging are used in neuroblastoma. One paper [50] reported the use of mIBG single photon emission computed tomography image fusion with planning computed tomography scans to aid target volume definition, and found it to be feasible. There is no evidence that it is of value.

A study of four-dimensional computed tomography imaging for radiotherapy planning has shown that internal organ motion varies between patients and that its routine use with individualised planning would permit greater precision [51].

It has been shown that intensity-modulated radiotherapy has the potential to achieve better dosimetry with regard to coverage of the target volume and organ at risk

Table 3
Is there evidence for a dose–response relationship? Assessment of the quality of the evidence. GRADE certainty low

Reference	CEBM 2011	ROBINS-I
Haas Kogan *et al.* [24]	Step 2	Low risk of bias
Von Almen *et al.* [40]	Step 3	Moderate risk of bias
Jacobson *et al.* [37]	Step 4	Serious risk of bias
Halperin and Cox [38]	Step 4	Serious risk of bias
Sibley *et al.* [39]	Step 4	Serious risk of bias
Casey *et al.* [41]	Step 4	Serious risk of bias

GRADE, Grading of Recommendations, Assessment, Development and Evaluations. CEBM, Centre for Evidence-based Medicine; ROBINS-I, Risk of Bias in Non-randomised Studies – of Interventions.

dose constraints than conventional radiotherapy [52–54]. Several small case series have been published showing feasibility and satisfactory early outcomes [55,56].

One team explored cone beam computed tomography in image-guided radiotherapy, showing that this facilitates the use of a smaller clinical target volume to planning target volume margin, thereby reducing exposure to organs at risk [57,58].

Proton beam radiotherapy has increasing clinical availability, and dosimetric advantages have been shown. Most studies reported in neuroblastoma are either small planning studies [59,60] or small clinical series [61–63]. We conclude that the dosimetry is more favourable in some but not all cases, and that treatment is feasible.

A methodology for international multicentre retrospective radiotherapy quality assurance in neuroblastoma has been described [64], and its use in 100 patients shows that protocol deviations are common [65]. Evidence that protocol deviations may lead to worse clinical outcomes has not yet been published in neuroblastoma, but this work has led to the establishment of the International Society of Paediatric Oncology (SIOP)-Europe Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials (QUARTET) project, which will provide a prospective radiotherapy quality review [66].

Discussion

Neuroblastoma is a radiosensitive tumour, and there is a long history of the use of radiotherapy in high-risk neuroblastoma. In diseases with a poor prognosis there is an understandable tendency to use every available treatment in an attempt to improve outcomes. However, high-risk neuroblastoma is not a homogeneous entity, and there are several distinct subgroups. Indisputable evidence that radiotherapy confers a survival benefit in high-risk neuroblastoma as a whole, and in each of its categories, is missing.

It is clear that most investigators believe that radiotherapy confers benefit, although not always in every case. Although there is evidence that radiotherapy has a biological effect, it is less clear that radiotherapy to the tumour bed confers a survival benefit, especially in patients with stage M disease following complete surgery in the context of modern systemic therapy.

A well-designed randomised trial with careful stopping rules could explore whether radiotherapy can safely be omitted in a subgroup of patients, for example those with completely resected, stage M, *MYCN* non-amplified tumours with a complete response to chemotherapy, potentially sparing them the adverse late effects of treatment without detriment.

Although there are some suggestions that a higher dose may be more effective, especially in the setting of gross residual disease after surgery, hard evidence that a higher dose would be beneficial is lacking. A randomised phase III trial comparing 21 Gy and 36 Gy after incomplete surgery is being developed by SIOPEN, and a randomised phase II trial is in progress in the UK as a pilot for this [67].

Lack of control of metastatic disease is a major cause of treatment failure and mortality in high-risk neuroblastoma. We have identified no good-quality prospective studies of radiotherapy to metastatic sites in children with neuroblastoma. There is a diversity of practice in this area. Despite some indications that metastatic site radiotherapy may be helpful, there is no clear evidence that it is a valuable intervention. There is a definite need for high-quality prospective research in this area of practice.

Newer techniques for radiotherapy planning and treatment in neuroblastoma should not be assumed to be better, but their potential benefits should be evaluated in well-designed prospective clinical studies that minimise the effect of bias.

Prospective randomised trials addressing, for example, the need for tumour bed radiotherapy in stage M neuroblastoma following complete resection; dose escalation in patients with residual disease; metastatic site irradiation; are needed. In paediatric oncology clinical trials, randomised studies aimed at defining and refining the place of radiotherapy should have as much of a place as those investigating systemic therapies.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

M.N. Gaze is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

[1] Monclair T, Brodeur GM, Ambros PF, Brisse HJ, Cecchetto G, Holmes K, *et al*. The International Neuroblastoma Risk Group (INRG) staging system: an INRG Task Force report. *J Clin Oncol* 2009;27:298–303. https://doi.org/10.1200/JCO.2008.16.6876.

[2] Cohn SL, Pearson ADJ, London WB, Monclair T, Ambros PF, Brodeur GM, *et al*. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *J Clin Oncol* 2009;27:289–297. https://doi.org/10.1200/JCO.2008.16.6785.

[3] Morgenstern DA, Pötschger U, Moreno L, Papadakis V, Owens C, Ash S, *et al*. Risk stratification of high-risk metastatic neuroblastoma: a report from the HR-NBL-1/SIOPEN study. *Pediatr Blood Cancer* 2018 Jul;17:e27363. https://doi.org/10.1002/pbc.27363.

[4] Gains J, Mandeville H, Cork N, Brock P, Gaze M. Ten challenges in the management of neuroblastoma. *Future Oncol* 2012;8:839–858. https://doi.org/10.2217/fon.12.70.

[5] Matthay KK, Maris JM, Schleiermacher G, Nakagawara A, Mackall CL, Diller L, *et al*. Neuroblastoma. *Nat Rev Dis Primers* 2016;2:16078. https://doi.org/10.1038/nrdp.2016.78.

[6] Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, *et al*. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a Children's Oncology Group study. *J Clin Oncol* 2009;27:1007–1013.
[7] Pritchard J, Cotterill SJ, Germond SM, Imeson J, de Kraker J, Jones DR. High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group. *Pediatr Blood Cancer* 2005;44:348–357.
[8] Berthold F, Boos J, Burdach S, Erttmann R, Henze G, Klingebiel T, *et al*. Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial. *Lancet Oncol* 2005;6:649–658.
[9] Ladenstein R, Pötschger U, Pearson ADJ, Brock P, Luksch R, Castel V, *et al*. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol* 2017;18:500–514. https://doi.org/10.1016/S1470-2045(17)30070-0.
[10] Gains JE, Bomanji JB, Fersht NL, Sullivan T, D'Souza D, Sullivan KP, *et al*. ^{177}Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. *J Nucl Med* 2011;52:1041–1047. https://doi.org/10.2967/jnumed.110.085100.
[11] Wilson JS, Gains JE, Moroz V, Wheatley K, Gaze MN. A systematic review of ^{131}I-meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. *Eur J Cancer* 2014;50:801–815. https://doi.org/10.1016/j.ejca.2013.11.016.
[12] Caussa L, Hijal T, Michon J, Helfre S. Role of palliative radiotherapy in the management of metastatic pediatric neuroblastoma: a retrospective single-institution study. *Int J Radiat Oncol Biol Phys* 2011;79:214–219. https://doi.org/10.1016/j.ijrobp.2009.10.031.
[13] https://www.cebm.net/2016/05/ocebm-levels-of-evidence. [Accessed 24 November 2018].
[14] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.
[15] Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
[16] Robinson KA, Saldanha IJ, McKoy NA. Development of a framework to identify research gaps from systematic reviews. *J Clin Epidemiol* 2011;64:1325–1330. https://doi.org/10.1016/j.jclinepi.2011.06.009.
[17] https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade. [Accessed 24 November 2011].
[18] Jairam V, Roberts KB, Yu JB. Historical trends in the use of radiation therapy for pediatric cancers: 1973–2008. *Int J Radiat Oncol Biol Phys* 2013;85:e151–e155. https://doi.org/10.1016/j.ijrobp.2012.10.007.
[19] Sultan I, Ghandour K, Al-Jumaily U, Hashem S, Rodriguez-Galindo C. Local control of the primary tumour in metastatic neuroblastoma. *Eur J Cancer* 2009;45:1728–1732. https://doi.org/10.1016/j.ejca.2009.04.021.
[20] Gutierrez JC, Fischer AC, Sola JE, Perez EA, Koniaris LG. Markedly improving survival of neuroblastoma: a 30-year analysis of 1,646 patients. *Pediatr Surg Int* 2007;23:637–646. https://doi.org/10.1007/s00383-007-1933-7.
[21] Pai Panandiker AS, McGregor L, Krasin MJ, Wu S, Xiong X, Merchant TE. Locoregional tumor progression after radiation therapy influences overall survival in pediatric patients with neuroblastoma. *Int J Radiat Oncol Biol Phys* 2010;76:1161–1165. https://doi.org/10.1016/j.ijrobp.2009.03.068.
[22] Castleberry RP, Kun LE, Shuster JJ, Altshuler G, Smith IE, Nitschke R, *et al*. Radiotherapy improves the outlook for patients older than 1 year with Pediatric Oncology Group stage C neuroblastoma. *J Clin Oncol* 1991;9:789–795. https://doi.org/10.1200/JCO.1991.9.5.789.
[23] Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, *et al*. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *N Engl J Med* 1999;341:1165–1173. https://doi.org/10.1056/NEJM199910143411601.
[24] Haas-Kogan DA, Swift PS, Selch M, Haase GM, Seeger RC, Gerbing RB, *et al*. Impact of radiotherapy for high-risk neuroblastoma: a Children's Cancer Group study. *Int J Radiat Oncol Biol Phys* 2003;56:28–39.
[25] Simon T, Hero B, Bongartz R, Schmidt M, Müller RP, Berthold F. Intensified external-beam radiation therapy improves the outcome of stage 4 neuroblastoma in children > 1 year with residual local disease. *Strahlenther Onkol* 2006;182:389–394. https://doi.org/10.1007/s00066-006-1498-8.
[26] Robbins JR, Krasin MJ, Pai Panandiker AS, Watkins A, Wu J, Santana VM, *et al*. Radiation therapy as part of local control of metastatic neuroblastoma: the St Jude Children's Research Hospital experience. *J Pediatr Surg* 2010;45:678–686. https://doi.org/10.1016/j.jpedsurg.2009.11.003.
[27] Laprie A, Michon J, Hartmann O, Munzer C, Leclaire M-D, Coze C, *et al*. High-dose chemotherapy followed by locoregional irradiation improves the outcome of patients with international neuroblastoma staging system Stage II and III neuroblastoma with MYCN amplification. *Cancer* 2004;101:1081–1089. https://doi.org/10.1002/cncr.20453.
[28] De Ioris MA, Crocoli A, Contoli B, Garganese MC, Natali G, Tomà P, *et al*. Local control in metastatic neuroblastoma in children over 1 year of age. *BMC Cancer* 2015;15:79. https://doi.org/10.1186/s12885-015-1082-7.
[29] Wolden SL, Gollamudi SV, Kushner BH, LaQuaglia M, Kramer K, Rosen N, *et al*. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000;46:969–974.
[30] Kushner BH, Wolden S, LaQuaglia MP, Kramer K, Verbel D, Heller G, *et al*. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. *J Clin Oncol* 2001;19:2821–2828. https://doi.org/10.1200/JCO.2001.19.11.2821.
[31] Bradfield SM, Douglas JG, Hawkins DS, Sanders JE, Park JR. Fractionated low-dose radiotherapy after myeloablative stem cell transplantation for local control in patients with high-risk neuroblastoma. *Cancer* 2004;100:1268–1275. https://doi.org/10.1002/cncr.20091.
[32] Marcus KJ, Shamberger R, Litman H, von Allmen D, Grupp SA, Nancarrow CM, *et al*. Primary tumor control in patients with stage 3/4 unfavorable neuroblastoma treated with tandem double autologous stem cell transplants. *J Pediatr Hematol Oncol* 2003;25:934–940.
[33] Gatcombe HG, Marcus Jr RB, Katzenstein HM, Tighiouart M, Esiashvili N. Excellent local control from radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2009;74:1549–1554. https://doi.org/10.1016/j.ijrobp.2008.10.069.
[34] Modak S, Kushner BH, LaQuaglia MP, Kramer K, Cheung NK. Management and outcome of stage 3 neuroblastoma. *Eur J Cancer* 2009;45:90–98. https://doi.org/10.1016/j.ejca.2008.09.016.

[35] Casey DL, Kushner BH, Cheung NK, Modak S, LaQuaglia MP, Wolden SL. Local control with 21-Gy radiation therapy for high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2016;96:393–400. https://doi.org/10.1016/j.ijrobp.2016.05.020.

[36] Ferris MJ, Danish H, Switchenko JM, Deng C, George BA, Goldsmith KC, *et al*. Favorable Local Control from consolidative radiation therapy in high-risk neuroblastoma despite gross residual disease, positive margins, or nodal involvement. *Int J Radiat Oncol Biol Phys* 2017;97(4):806–812. https://doi.org/10.1016/j.ijrobp.2016.11.043.

[37] Jacobson GM, Sause WT, O'Brien RT. Dose response analysis of pediatric neuroblastoma to megavoltage radiation. *Am J Clin Oncol* 1984;7:693–697.

[38] Halperin EC, Cox EB. Radiation therapy in the management of neuroblastoma: the Duke University Medical Center experience 1967–1984. *Int J Radiat Oncol Biol Phys* 1986;12:1829–1837.

[39] Sibley GS, Mundt AJ, Goldman S, Nachman J, Reft C, Weichselbaum RR, *et al*. Patterns of failure following total body irradiation and bone marrow transplantation with or without a radiotherapy boost for advanced neuroblastoma. *Int J Radiat Oncol Biol Phys* 1995;32:1127–1135.

[40] von Allmen D, Grupp S, Diller L, Marcus K, Ecklund K, Meyer J, *et al*. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. *J Pediatr Surg* 2005;40:936–941. https://doi.org/10.1016/j.jpedsurg.2005.03.008. discussion 941.

[41] Casey DL, Kushner BH, Cheung NV, Modak S, LaQuaglia MP, Wolden SL. Dose-escalation is needed for gross disease in high-risk neuroblastoma. *Pediatr Blood Cancer* 2018;65:e27009. https://doi.org/10.1002/pbc.27009.

[42] Casey DL, Pitter KL, Kushner BH, Cheung N-KV, Modak S, LaQualia MP, *et al*. Radiation therapy to sites of metastatic disease as part of consolidation in high-risk neuroblastoma: can long-term control be achieved? *Int J Radiat Oncol Biol Phys* 2018;100:1204–1209. https://doi.org/10.1016/j.ijrobp.2018.01.008.

[43] Li R, Polishchuk A, DuBois S, Hawkins R, Lee SW, Bagatell R, *et al*. Patterns of relapse in high-risk neuroblastoma patients treated with and without total body irradiation. *Int J Radiat Oncol Biol Phys* 2017;97:270–277. https://doi.org/10.1016/j.ijrobp.2016.10.047.

[44] Mazloom A, Louis CU, Nuchtern J, Kim E, Russell H, Allen-Rhoades W, *et al*. Radiation therapy to the primary and postinduction chemotherapy MIBG-avid sites in high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2014;90:858–862. https://doi.org/10.1016/j.ijrobp.2014.07.019.

[45] Kandula S, Prabhu RS, Nanda R, Switchenko JM, Cash T, Qayed M, *et al*. Outcomes after radiation therapy to metastatic sites in patients with stage 4 neuroblastoma. *J Pediatr Hematol Oncol* 2015;37:175–180. https://doi.org/10.1097/MPH.0000000000000264.

[46] Polishchuk AL, Li R, Hill-Kayser C, Little A, Hawkins RA, Hamilton J, *et al*. Likelihood of bone recurrence in prior sites of metastasis in patients with high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2014;89:839–845. https://doi.org/10.1016/j.ijrobp.2014.04.004.

[47] Wolden SL, Barker CA, Kushner BH, Bodduluri H, Della-Biancia C, Kramer K, *et al*. Brain-sparing radiotherapy for neuroblastoma skull metastases. *Pediatr Blood Cancer* 2008;50:1163–1168.

[48] Kushner BH, Cheung NK, Barker CA, Kramer K, Modak S, Yataghene K, *et al*. Hyperfractionated low-dose (21 Gy) radiotherapy for cranial skeletal metastases in patients with high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2009;75:1181–1186. https://doi.org/10.1016/j.ijrobp.2008.12.026.

[49] Sangthawan D, DesRosiers PM, Randall ME, Robertson K, Goebel S, Fallon R. Relapse in the skull after myeloablative therapy for high-risk neuroblastoma. *Pediatr Hematol Oncol* 2003;20:23–30.

[50] Fenig E, Mishaeli M, Yerushalmi R, Sever ZB, Ash S, Kornreich L, *et al*. Treatment of neuroblastoma using the fused imaging guided radiotherapy (FIGURA) system. *Clin Nucl Med* 2006;31:256–258. https://doi.org/10.1097/01.rlu.0000214481.43868.bf.

[51] Kannan S, Teo BK, Solberg T, Hill-Kayser C. Organ motion in pediatric high-risk neuroblastoma patients using four-dimensional computed tomography. *J Appl Clin Med Phys* 2017;18(1):107–114. https://doi.org/10.1002/acm2.12012.

[52] Paulino AC, Ferenci MS, Chiang KY, Nowlan AW, Marcus Jr RB. Comparison of conventional to intensity modulated radiation therapy for abdominal neuroblastoma. *Pediatr Blood Cancer* 2006;46:739–744. https://doi.org/10.1002/pbc.20456.

[53] Gains JE, Stacey C, Rosenberg I, Mandeville HC, Chang Y-C, D'Souza D, *et al*. Intensity-modulated arc therapy to improve radiation dose delivery in the treatment of abdominal neuroblastoma. *Future Oncol* 2013;9:439–449. https://doi.org/10.2217/fon.12.199.

[54] Beneyton V, Niederst C, Vigneron C, Meyer P, Becmeur F, Marcellin L, *et al*. Comparison of the dosimetries of 3-dimensional radiotherapy (3D-RT) with linear accelerator and intensity modulated radiotherapy (IMRT) with helical tomotherapy in children irradiated for neuroblastoma. *BMC Med Phys* 2012;12:2. https://doi.org/10.1186/1756-6649-12-2.

[55] Nazmy MS, Khafaga Y. Clinical experience in pediatric neuroblastoma intensity modulated radiotherapy. *J Egypt Natl Cancer Inst* 2012;24:185–189. https://doi.org/10.1016/j.jnci.2012.10.001.

[56] Pai Panandiker AS, Beltran C, Billups CA, McGregor LM, Furman WL, Davidoff AM. Intensity modulated radiation therapy provides excellent local control in high-risk abdominal neuroblastoma. *Pediatr Blood Cancer* 2013;60:761–765. https://doi.org/10.1002/pbc.24350.

[57] Beltran C, Pai Panandiker AS, Krasin MJ, Merchant TE. Daily image-guided localization for neuroblastoma. *J Appl Clin Med Phys* 2010;11:3388.

[58] Pai Panandiker AS, Beltran C, Gray J, Hua C. Methods for image guided and intensity modulated radiation therapy in high-risk abdominal neuroblastoma. *Pract Radiat Oncol* 2013;3:107–114. https://doi.org/10.1016/j.prro.2012.04.002.

[59] Hillbrand M, Georg D, Gadner H, Pötter R, Dieckmann K. Abdominal cancer during early childhood: a dosimetric comparison of proton beams to standard and advanced photon radiotherapy. *Radiother Oncol* 2008;89:141–149. https://doi.org/10.1016/j.radonc.2008.06.012.

[60] Fuji H, Schneider U, Ishida Y, Konno M, Yamashita H, Kase Y, *et al*. Assessment of organ dose reduction and secondary cancer risk associated with the use of proton beam therapy and intensity modulated radiation therapy in treatment of neuroblastomas. *Radiat Oncol* 2013;8:255. https://doi.org/10.1186/1748-717X-8-255.

[61] Hattangadi JA, Rombi B, Yock TI, Broussard G, Friedmann AM, Huang M, *et al*. Proton radiotherapy for high-risk pediatric neuroblastoma: early outcomes and dose comparison. *Int J Radiat Oncol Biol Phys* 2012;83:1015–1022. https://doi.org/10.1016/j.ijrobp.2011.08.035.

[62] Oshiro Y, Mizumoto M, Okumura T, Sugahara S, Fukushima T, Ishikawa H, *et al*. Clinical results of proton beam therapy for

advanced neuroblastoma. *Radiat Oncol* 2013;8:142. https://doi.org/10.1186/1748-717X-8-142.

[63] Hill-Kayser C, Tochner Z, Both S, Lustig R, Reilly A, Balamuth N, *et al*. Proton versus photon radiation therapy for patients with high-risk neuroblastoma: the need for a customized approach. *Pediatr Blood Cancer* 2013;60: 1606–1611. https://doi.org/10.1002/pbc.24606.

[64] Gaze MN, Boterberg T, Dieckmann K, Habrand J-L, Helfré S, Peylan-Ramu N, *et al*. Development of an electronic database for quality assurance of radiotherapy in the International Society of Paediatric Oncology (Europe) high risk neuroblastoma study. *Radiother Oncol* 2010;97:593–595. https://doi.org/10.1016/j.radonc.2010.08.017.

[65] Gaze MN, Boterberg T, Dieckmann K, Hörmann M, Gains JE, Sullivan KP, *et al*. Results of a quality assurance review of external beam radiation therapy in the International Society of Paediatric Oncology (Europe) Neuroblastoma Group's High-risk Neuroblastoma Trial: a SIOPEN study. *Int J Radiat Oncol Biol Phys* 2013;85:170–174. https://doi.org/10.1016/j.ijrobp.2012.05.004.

[66] https://www.siope.eu/2016/05/25/quartet-project. [Accessed 24 November 2018].

[67] https://doi.org/10.1186/ISRCTN10746820. [Accessed 24 November 2018].