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REVIEW ARTICLE

A scoping review of patient selection methods for proton therapy

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Abstract

The aim was to explore various national and international clinical decision-making tools and dose comparison methods used for selecting cancer patients for proton versus X-ray radiation therapy. To address this aim, a literature search using defined scoping review methods was performed in Medline and Embase databases as well as grey literature. Articles published between 1 January 2015 and 4 August 2020 and those that clearly stated methods of proton versus X-ray therapy patient selection and those published in English were eligible for inclusion. In total, 321 studies were identified of which 49 articles met the study's inclusion criteria representing 13 countries. Six different clinical decision-making tools and 14 dose comparison methods were identified, demonstrating variability within countries and internationally. Proton therapy was indicated for all paediatric patients except those with lymphoma and re-irradiation where individualised model-based selection was required. The most commonly reported patient selection tools included the Normal Tissue Complication Probability model, followed by cost-effectiveness modelling and dosimetry comparison. Model-based selection methods were most commonly applied for head and neck clinical indications in adult cohorts (48% of studies). While no 'Gold Standard' currently exists for proton therapy patient selection with variations evidenced globally, some of the patient selection methods identified in this review can be used to inform future practice in Australia. As literature was not identified from all countries where proton therapy centres are available, further research is needed to evaluate patient selection methods in these jurisdictions for a comprehensive overview.

Introduction

External beam radiation therapy (EBRT) uses radiation delivered in equivalent daily fractions over several treatments to kill cancer cells. Conventional EBRT, available worldwide, employs high-energy X-rays.[1] Conversely, particle therapy uses high-energy charged particles, most commonly protons. As of February 2021, there are 95 proton therapy (PT) centres currently operational worldwide.[2] PT's main benefit is a rapid dose fall-off beyond the peak dose or Bragg Peak, which spares healthy tissue, whereas X-rays irradiate normal tissues before and after the tumour.[3] PT can offer increased tumour control as healthy tissue can be avoided enabling dose escalation to some tumours, translating to increased loco-regional control for select patients.[3,4]

While both modalities offer effective EBRT cancer treatment, PT can reduce normal tissue doses compared to conventional X-ray therapy, thus potentially decreasing radiation-induced complications such as a second primary malignancy.[5–7] Despite this, not all patients requiring radiation therapy are offered PT due to patient accessibility, cost, equitable dosimetry with X-ray therapy and uncertainty regarding clinical outcomes following treatment.[3,4]

PT is more costly compared to the current, best available conventional radiation. Peeters et al.[8] estimate

PT is four times as expensive as X-ray treatment due to higher capital, equipment, quality assurance and operational costs. As PT carries a higher upfront financial burden, appropriate patient selection becomes critical, especially for jurisdictions like Australia where health-related goods and services are Government-subsidised. The number of Australian patients likely to benefit from PT compared to conventional RT is estimated to be between 5–15%.[9]

Currently, the best available evidence for patients being referred to PT is from retrospective analyses of small single-institutional studies, patient case studies, dosimetric studies or literature reviews.[5,10] The lack of 'Gold Standard' randomised control trial data is attributed to methodological and ethical concerns given PT's limited availability, high cost, limited long-term complication data and difficulties with appropriate, blinded patient allocation.[11,12] PT has been reported to be more cost-effective compared to conventional X-ray therapy in paediatric patients diagnosed with central nervous system tumours, some patients with head and neck tumours, certain breast cancer patients at high risk of radiation-induced cardiac events and those diagnosed with hepatocellular tumours.[5,10,13] For other clinical indications such as prostate cancer, the cost-effective treatments are in favour of conventional radiation therapy.[4,6,13,14]

As radiation therapy patient cohorts are heterogeneous, the allocation of PT resources can be difficult and does not always follow a 'one-size fits all' approach.[13,15,16] A recent systematic review found that particle therapies offer equal or improved toxicity outcomes compared with conventional radiation therapy for a range of cancer diagnoses,[17] yet it is unknown to what extent the benefits apply to all cancer patients receiving radiation therapy. Patient selection must therefore be individualised to ensure that patients most likely to benefit from PT are being referred for PT. This is of particular importance in the Australian context, as the first proton therapy centre is planned to open in Adelaide in the coming years.

To facilitate the difficult decision-making related to patient allocation for PT, clinical decision-making tools have been developed to assist clinicians in matching appropriate treatment based on patient-specific factors (e.g. patient diagnosis, age [paediatric or adult], performance status and prognosis).[18–22] Other approaches include dose comparison methods, where comparison is made between proton and X-ray radiation dose distributions, including their associated tumour control and normal tissue complication probabilities prior to recommending the treatment modality.[23–26]

Clinical decision-making tools and dose comparison methods are used exclusively or in combination.[16,27] Anecdotally, variations in patient selection methods exist among countries due to the clinical availability of PT and whether PT centres are publicly or privately funded. In Australia, there is a publically funded Medical Treatment Overseas Program (MTOP) by the Medicare Benefits Scheme. The MTOP application process includes both clinical decision-making tool (indications list) and dose distribution comparisons provided by the National Proton versus Photon Comparative Planning service[27]. Patients are evaluated on a patient-specific basis regarding their eligibility to receive funding to travel internationally to receive PT.

To our knowledge, no study has synthesised and pooled specific clinical decision-making and dose comparison methods literature for PT patient selection. Given the gap in knowledge regarding how PT patient selection occurs internationally, the aim of this scoping review was to identify the current global practice of PT patient selection to better inform future practice and decision-making in Australia. The underpinning research question was 'What patient selection methods are used globally to select patients for proton versus X-ray therapies?'. The question was broad enough to capture global PT patient selection practices, however remained specific to PT excluding other heavy-ion therapies (e.g. carbon-ion).

Methods

Literature search

This study followed established scoping review methods.[28,29] A scoping review rather than a systematic review was selected as this would ensure all white and grey literature surrounding PT was captured. A systematic literature search was performed in Medline and Embase databases for literature published from 1 January 2015 to 4 August 2020, to identify the methods used for PT patient selection including clinical decision-making tools and dose comparison methods. MeSH and regular keywords were applied to the databases to locate relevant papers. The full search strategy is shown in the Appendix S1. Key search terms included were 'Proton Therapy', 'Radiotherapy', 'Clinical Decision-Making', 'Decision Support Techniques', 'Computer-Assisted Decision-Making' and 'Patient Selection'. To complement the database searches and to broaden the scope of available publication types, a manual search of the reference lists of included papers was performed. In addition, a broad web search was performed for grey literature such as government publications, white papers and publications from professional societies, for example clinical indications lists. An additional 20 publications were identified through these methods.

Subsequent to database searches, the literature was exported into Covidence (Covidence systematic review software, Veritas Health Innovation, www.covidence.org). Covidence enables title and abstract screening, full-text screening and data extraction to be streamlined with remote accessibility by multiple researchers and enables online record keeping via password-protected accounts and flexibility in sharing privileges.

Study election, eligibility and screening

Publications were selected if they fit the study's eligibility criteria. All white and grey literature sources were included (e.g. government papers, conference abstracts). Publications were only included if they were human studies that included content on proton and photon therapies for cancer, were published from 2015 onwards and were in English. Grey and white literature as well as abstracts and full-text articles were all included in this study to capture all publications focussing on clinical decision-making tools and dose comparison methods, especially where novel techniques have not yet been published in peer-reviewed articles. The inclusion of publications from January 2015 to August 2020 ensured that only the most current X-ray (e.g. intensity-modulated radiation therapy [IMRT], volumetric modulated arc therapy [VMAT]) and proton (e.g. pencil beam scanning) technologies were captured and evaluated. Languages other than English were excluded due to issues of locating and translating these studies.

Records obtained from the initial search were exported into Covidence and screened by the first and last authors (NZ and MS). Both authors independently removed duplicates (n = 22) and performed a title and abstract screening for the remaining papers using the above criteria. The authors compared screenings, discussed conflicts and reached agreement regarding inclusion by consensus. Publications included after the title and abstract screen proceeded to full-text review. Once full-text articles were retrieved, further independent assessment for inclusion was performed by each researcher, any conflicts were discussed with a rationale presented for inclusion/exclusion, and upon consensus, the publications were either included or assigned a rationale for exclusion in Covidence.

Data extraction

Relevant data from included studies were extracted into Covidence's data extraction page, including authors, year of publication, study design (e.g. systematic reviews, prospective cohort studies, retrospective cohort studies, case-control studies), country, treatment site (e.g. brain, head and neck, lung), population (paediatric or adult), PT technique (passive scattering or pencil beam scanning), total sample size in included study, type of clinical decision-making tool, type of dose comparison method and advantages and disadvantages of the patient selection method (if reported). All data were exclusively obtained from the full-text publications. It was not possible to obtain additional data by contacting investigators or by any other means. Once data extraction was complete, the PRISMA flow diagram and extracted results were exported from Covidence into a Microsoft Excel© (version 16.39, Microsoft Corporation, 2020) spreadsheet for analysis.

Data handling and bias

Following data extraction, content analysis and data reduction were performed by grouping different studies into categories (samples, research design, patient selection tools, etc.). As this was a scoping review, critical appraisal and risk of bias assessment within and across studies were not performed; however, quality of each publication was assessed subjectively by two authors. The overall data were analysed using descriptive synthesis.

Results

A total of 49 publications were included in this study. Figure 1 details the study selection process in the format of a PRISMA diagram.

Publications addressing PT patient selection have been increasing since 2015. In order of the strength of evidence one publication was a systematic review,[13] five were government or medical college clinical indication lists,[18–22] eight were literature reviews,[4–6,10,15,30–32] five were prospective studies,[14,33–36] 28 were retrospective studies,[3,7,11,12,16,23,25,26,37–56] one was a case-control study,[57] and one was an expert opinion[58]. Thirty-five publications were full-text articles, nine were conference abstracts, and five were government or medical college clinical practice guidelines. Content within the abstracts provided novel insight into PT patient selection methods where information had not been published elsewhere but could not be disregarded.

In total, 33 publications reported methods for PT patient selection in adults, nine publications reported on both paediatric, and adult cohorts and seven publications reported methods for PT patient selection in paediatrics. PT patient selection methods from 13 countries were identified. Of these publications, nine countries have PT clinically operational, three countries have PT centres currently under construction or in planning, and one country had no association with PT facilities.[2] Ten countries who currently have PT operational including Austria, Belgium, Czech Republic, India, Italy, Japan,

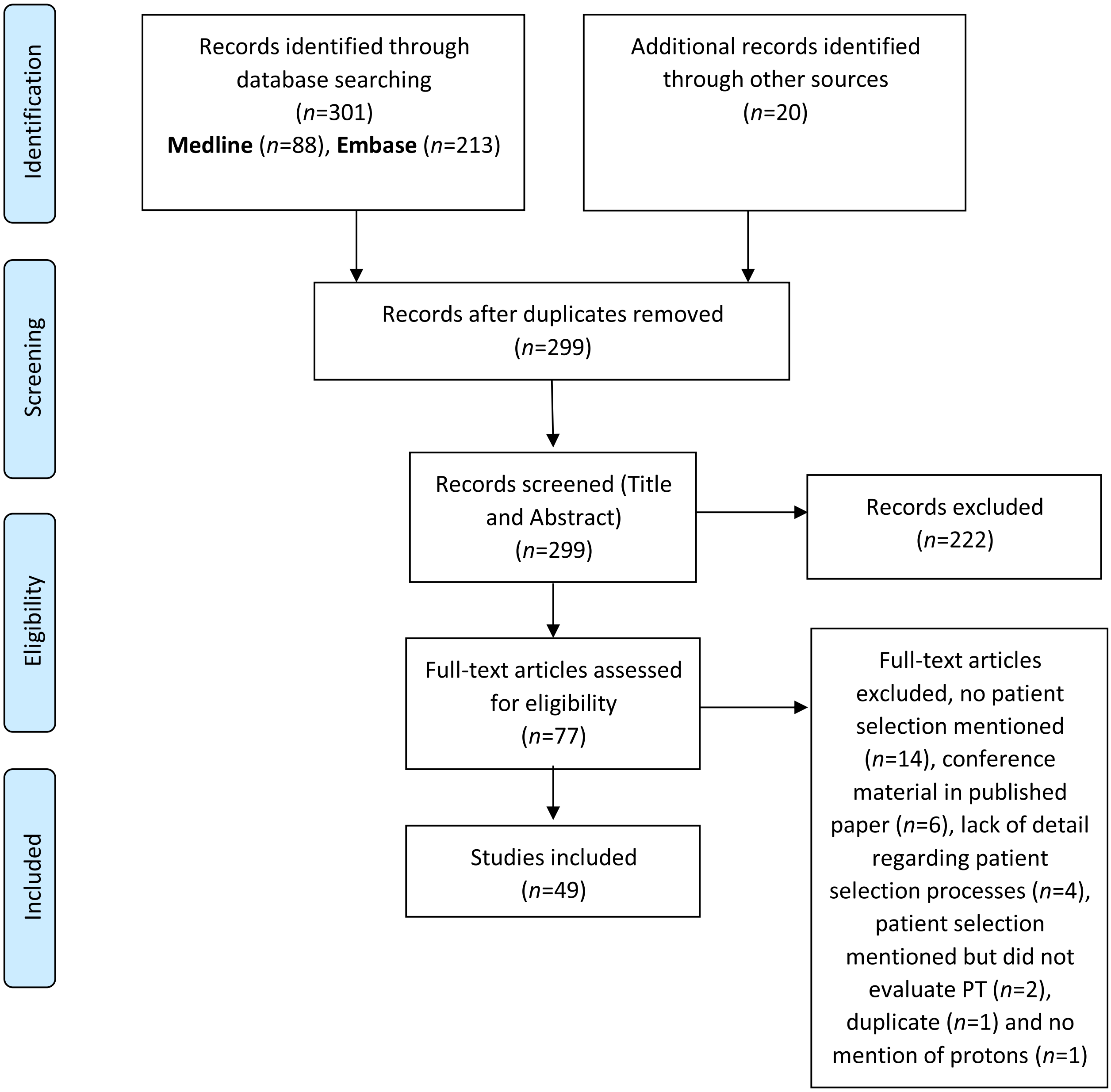

Figure 1. Selection of studies for inclusion in the review in the format of a PRISMA diagram.

Poland, Russia, South Korea and Taiwan, were not represented in the identified literature.

Cancer of the head and neck was the most reported clinical indication that PT patient selection was performed on (48% of studies), followed by: brain, prostate, lung, breast, lymphoma, paediatric, skull base, liver, cervix and endometrium. Five diagnosis/clinical indications lists were identified, and they were from the United States (US),[22] United Kingdom (UK),[18] Canada,[21] The Netherlands,[20] Australia and New Zealand.[19] An overview of the clinical decision-making tools and dose comparison methods identified in the scoping review are shown in Table 1.

Paediatrics

Clinical decision-making

Table 2 compares the paediatric clinical indications lists of five countries: the United Kingdom (UK),[18] United

Table 1. Overview of clinical decision-making tools and dose comparison methods used for PT patient selection

Method	Description	Benefits	Limitations
Clinical decision-making tools			
Informed decision-making[34]	-Clinicians explain all available treatment methods to patients. Patients select between PT and X-ray	-Patient's decisions are unrestricted as they are aware of all available treatment options	-Time intensive -Patient eligibility for insurance reimbursement or ability to self-fund treatments
Diagnosis/clinical indications list[18-22]	-Consensus-based list of diagnoses eligible for PT	-Assists department workload	-May exclude patients who could benefit from PT
Pre-chemotherapy characteristics[7]	-Patient is selected based on chemotherapy characteristics	NR	-Sample size of the study was low (n = 21)
Multi-disciplinary team consensus[38]	-A multi-disciplinary team convenes to make treatment decisions	-Personalisation	NR
Cost-effectiveness[13,59]	-Patients allocated to PT based on long-term cost-effectiveness	-Cost savings to Government and/or patient	-Adverse side effect costs are uncertain
Dose comparison methods			
Comparative planning / Dosimetry[60]	-Comparison of proton and X-ray computed dose distributions	-Cost-effective -Toxicity analysis performed	-Time intensive as multiple plans need to be generated -Uncertainty in comparison of non-robustly optimised proton plans
NTCP[12,26,37,43,52]	-NTCPs are compared between plans	-Decreased resources -Decreased workload -Efficient -Useful when clinical trial data is unavailable	-RBE uncertainties -Inter-patient variation in radio-sensitivity -Time intensive as multiple plans need to be generated -Not all NTCP models are valid for protons
Knowledge-based DVH predictions[3]	-Organ toxicity endpoints compared between plans	-Individualised -Semi-automated -Transparent process -Efficient (<1 min)	-RapidPlan is only intended for protons -Comparing 'matured' VMAT with newer PT -Dosimetric comparisons do not always translate to clinical reductions in toxicities
Influence diagram[40]	-An influence diagram was created for non-small cell lung cancer patients, to model radiation delivery, associated 6-month pneumonitis/ oesophagitis rates and overall costs	-Computationally efficient	-Patient factors such as costs associated with hospitalisation, needing a ventilator, time lost from work and further comorbidities were not accounted for -QoL not considered
Predictive modelling via QuickMatch[49]	-Plan prediction software (QuickMatch) predicted radiation doses to PTVs and OARs	-Objective method -Results in quality improvement -Improved workflow	-Novel technique, requires further validation -Time intensive
ReCompare[54]	-Uses client-server-based software for conventional radiation therapy centres to have plan comparisons completed with PT centres	-Creates networks between PT and conventional radiation therapy centres -Helps to support and increase skill base of staff	-Created proton plans cannot be used for treatment due to Hounsfield unit conversions and differences in patient positioning
Simulation model[53]	-A model developed for tracking individual patient's status of NTCP and GTV	NR	-HRQoL values were missing for few complication strategies
Geometric knowledge-based method[51]	-Computers use the geometric arrangement of tumour and organs to compare plans	-Computationally efficient -Less resource-intensive -Can be used for patient selection assessment by insurance companies	-RBE uncertainties

(*Continued*)

Table 1. Continued.

Method	Description	Benefits	Limitations
Radiobiological fuzzy Markov model[11,56]	-Markov modelling that considers uncertainties in radiobiological model parameters and planned dose	NR	NR
NTCP, EUD and mean lung dose[43]	-Prediction of late radiation lung damage using NTCP, EUD and the mean lung dose	NR	-RBE uncertainties
Hypothesis-generating model[45]	-The mean liver dose and the volume of liver minus GTV receiving <15Gy was compared between modalities	NR	NR
New-PST[36]	-A model-based optimisation VMAT plan is created. Plan comparison is then performed on selected patients who exceed one of the three NTCP endpoints. A robust IMPT plan is optimised for selected patients. New-PST assumes a mean dose of 0Gy outside the PTV	-Cost-effective -Decreased workload -No patients wrongfully denied	-Time and resource-intensive
Risk analysis/long-term outcomes[10,32]	-A combination of NTCPs and outcome data are compared between modalities	NR	NR
Hybrid techniques			
PRODECIS[16]	Computer-generated model that selects modality based on dosimetry, toxicity levels and cost-effectiveness	-Individualised -Automatic -Dynamic selection of models based on tumour type -Can incorporate new insights -Quantitatively prioritise patients -Can be used as evidence for insurance companies	-Method in its early stage -Data security -Lack of case management -Plans must follow a strict protocol for the model to be effective -Markov model varies between countries -Previous interventions (surgery or chemotherapy) are not accounted for

DVH, dose volume histogram; EUD, equivalent uniform dose; GTV, gross tumour volume; HRQoL, health-related quality of life; min, minute; OAR, organ at risk; NR, not reported; NTCP, normal tissue complication probability; PRODECIS, proton decision support; PT, proton therapy; PTV, planning target volume; QoL, quality of life; RBE, relative biological effectiveness; VMAT, volumetric modulated arc therapy.

States (US),[22] Canada,[21] The Netherlands,[20] Australia and New Zealand.[19] PT was indicated for a majority of benign and malignant paediatric malignancies with consensus across all clinical indication lists for the following: base of skull and spinal chordomas and chondrosarcomas, intracranial germ cell tumours, rhabdomyosarcoma, Ewing sarcoma, optic pathway and other low-grade gliomas and craniopharyngiomas. Variations existed for other clinical indications as shown in Table 2.

Overall, PT was indicated for paediatric cohorts due to its cost-effectiveness owing to the minimisation of acute and late toxicities.[6,49] PT was also indicated for patients with neurofibromatosis type 1 (NF1) or other cancer predisposition risks in the UK[18] and United States[22] and those patients with an inherent cancer risk from genes such as *rb1* and *p53*.[5]

Dose comparison methods

Additional to the five clinical indications lists and literature review describing paediatric PT indications, six publications focussed on paediatric patient selection.[10,42–44,56,61] Of these, two assessed cost-effectiveness,[11,56] three used model-based NTCPs,[42–44] and one used a combination of model-based NTCPs, dosimetry and cost-effectiveness.[10] Five publications applied dose comparison methods to the brain[11,42–44,56] and one applied dose comparison methods to various anatomical sites.[10]

Adults

Clinical decision-making

Within the adult population, six different clinical decision-making tools were identified: Proton Decision

Table 2. Clinical indications for proton therapy in paediatric patients

Clinical Indication	COUNTRY/REGION †UK[18]	‡United States [22]	§Canada[21]	§Netherlands[20]	‡Australia & New Zealand[19]
Chordoma base of skull/spinal	[green]	[green]	[green]	[green]	[green]
Chondrosarcoma base of skull/spine	[green]	[green]	[green]	[green]	[green]
Craniopharyngioma	[green]	[green]	[green]	[green]	[green]
Ependymoma	[green]	[green]	[green]	[green]	[green]
Ewing sarcoma	[green]	[green]	[green]	[green]	[green]
Intracranial germ cell tumour	[green]	[green]	[green]	[green]	[green]
Optic pathway and other selected low-grade glioma	[green]	[green]	[green]	[green]	[green]
Rhabdomyosarcoma	[green] <10year	[green]	[green]	[green]	[green]
Medulloblastoma	NR	[green]	[green]	[green]	[green]
Pelvic sarcoma	[green]	[green]	[green]	[green]	NR
Pineal parenchymal tumours (*excluding pineoblastoma*)	[green]	[green]	[green]	[green]	NR
Retinoblastoma	[green]	[green]	NR	[green]	[green]
Intraocular melanoma	NR	[green]	[green]	NR	[green]
Primitive neuroectodermal tumours	NR	[green]	[green]	NR	NR
Re-irradiation	[green]	[green]	NR	[green]	[orange]
Spinal/paraspinal bone and soft tissue sarcoma (non-Ewing)	[green]	[green]	NR	NR	[green]
Children with NF1 and any other cancer predisposition syndrome requiring RT	[green]	[green]	NR	NR	NR
Esthesioneuroblastoma	[green]	NR	[green]	NR	NR
Intracranial arteriovenous malformation	NR	NR	[green]	NR	NR
Lymphoma	NR	[orange]	[green]	NR	[orange]
Nephroblastoma	NR	NR	NR	[green]	NR

NF1, neurofibromatosis type 1; NR, not reported; RT, radiation therapy. Shading: Green – PT is indicated; Orange – PT may be indicated (model-based selection required).
†Paediatric defined as <25 years.
‡Paediatric defined as <18 years.
§Paediatric defined as <16 years.

Support (PRODECIS),[16] informed decision-making,[34] clinical indications list,[6] pre-chemotherapy characteristics,[7] cost-effectiveness[4] and multi-disciplinary team consensus.[38]

Clinical indication lists were identified as the most commonly used clinical decision-making tool in adult cohorts, with full details as shown in Table 3. For adults, consensus across indications lists was only evident for base of skull, spinal chordomas and chondrosarcomas.[18–22] Variability was seen for all other tumour sites as well as for including re-irradiation.

Brain, skull base, ocular and head and neck tumours

PT for brain indications was variable in adult cohorts. Adeberg et al.[60] suggested PT should be indicated for parietal tumours and radioresistant glioblastoma as protons have a greater linear energy transfer compared with X-rays.

The comparison of clinical indication lists demonstrated clear consensus for recommending PT for skull base tumours.[18–22] This was substantiated if targets were in excess of 60 Gy, and/or multiple organs at risk (OARs) were nearby in order to spare normal tissues.[5,42] PT was also indicated for ocular tumours in the United States,[22] Canada,[21] Australia and New Zealand.[19] Verma et al.[13] found PT a cost-effective option for both of these tumour types.

For head and neck cancers, nasal cavity and paranasal sinus tumours were referred for PT in Canada,[21] nasopharyngeal carcinoma in the UK[18] and advanced and/or unresectable head and neck cancers in the United States.[22] PT may be cost-effective for some patients with head and neck cancers.[62]

Lung tumours

There was no clear consensus regarding whether proton therapy was indicated for lung cancer. In the United States, it was considered a model-based indication, meaning that to be indicated for PT, a dose comparison of a conventional X-ray and a proton plan must occur and treatment would be indicated for the most favourable

Table 3. Clinical indications for proton therapy in adults

Clinical Indication	Country/region: UK[18]	United States [22]	Canada[21]	Netherlands[20]	Australia & New Zealand[19]
Chondrosarcoma base of skull/spine	[green]	[green]	[green]	[green]	[green]
Chordoma base of skull/spine	[green]	[green]	[green]	[green]	[green]
Intraocular melanoma	[green]	[green]	[green]	NR	[green]
Craniopharyngioma	[green]	NR	[green]	[green]	NR
Optic pathway and other selected low-grade glioma	[green]	NR	[green]	[green]	NR
Spinal/paraspinal bone and soft tissue sarcoma (non-Ewing)	[green]	NR	[green]	NR	[green]
Ependymoma	NR	NR	[green]	[green]	NR
Hepatocellular cancer	NR	[green]	NR	NR	[green]
Intracranial arteriovenous malformation	[green]	NR	[green]	NR	NR
Lymphoma	NR	[orange]	[green]	<30years [green]	NR
Medulloblastoma	[green]	NR	NR	[green]	NR
Pelvic sarcoma	[green]	NR	NR	[green]	NR
Rhabdomyosarcoma	NR	NR	[green]	[green]	NR
Advanced and/or unresectable head and neck cancers	NR	[green]	NR	NR	NR
Esthesioneuroblastoma	[green]	NR	NR	NR	NR
Nasopharyngeal carcinoma	[green]	NR	NR	NR	NR
Nephroblastoma	NR	NR	NR	[green]	NR
Paranasal sinus or nasal cavity	NR	NR	[green]	NR	NR
Pineal parenchymal tumours (*excluding pineoblastoma*)	NR	NR	[green]	NR	NR
Primitive neuroectodermal tumours	NR	NR	[green]	NR	NR
Re-irradiation	NR	[green]	NR	NR	[orange]
Retinoblastoma	NR	NR	NR	[green]	NR
Oesophageal cancer	NR	[orange]	NR	NR	[orange]
Pancreatic cancer	NR	[orange]	NR	NR	[orange]
Prostate cancer	NR	No M [orange]	NR	NR	[red]
Lung cancer	NR	[orange]	NR	NR	[red]
Breast cancer	NR	[orange]	NR	NR	[red]

NR, not reported; M, metastases. Shading: Green – PT indicated; Orange – PT may be indicated (model-based selection required); Red-PT not indicated, use conventional X-ray RT.

plan, whereas in Australia and New Zealand PT for lung cancer was not deemed suitable.[19,22] Clinical indication lists from remaining countries did not report on lung cancer.[18,20,21] Based on other literature found in the scoping review, PT was recommended for patients with early-stage or locally advanced NSCLC patients at high risk of developing severe acute side effects (e.g. elderly),[10,31,40] patients with tumours located centrally and close to the brachial plexus, and patients whose tumours or nodal involvement overlapped with or was inferior to T7.[46] Verma et al.[13] and Smith et al.[63] alternatively found PT was not effective for early-stage lung cancer or low-risk groups where cost differences between conventional and PT were minimal.

Liver cancer

PT was indicated for hepatocellular carcinoma in Australia, New Zealand and United States.[19,22] PT may be cost-effective for select liver indications.[13] Gandhi et al. suggested PT was an option for dome and central tumours >3cm to allow maximum liver sparing and potentially reduce radiation toxicity, and any tumours >5cm if conventional radiation fails to achieve adequate coverage or exceeds the mean liver threshold.[45]

Breast cancer

PT was not indicated for patients with breast cancer, however, and was a model-based indication in the United States.[22] PT may be cost-effective for women with > 1 cardiac risk factor for mean heart dose >5 Gy[57] in well-selected breast cancer patients at increased risk for cardiovascular toxicity.[31]

Prostate cancer

PT was not indicated for prostate cancer, however, and is a possible model-based indication in the United States.[22] The literature was variable regarding prostate cancer indications and cost-effectiveness of PT. One paper reported that PT for prostate cancer was not cost-effective[4], whereas cost-effectiveness may be achieved for younger and favourable-risk prostate cancer patients.[6]

Lymphoma

Variability in PT for lymphoma patients existed; Canada indicates lymphoma for PT,[21] the Netherlands indicates PT for lymphoma in patients less than 30 years old,[20] and lymphoma is a model-based indication in the United States.[22] Ntentas et al.[7] recommended PT for Hodgkin Lymphoma (HL) patients where the clinical target volume (CTV) extends below the seventh thoracic level, female patients with axillary disease and patients who have more extensive disease and hence larger PTVs. Tseng et al.[32] similarly recommended PT for lymphoma patients with axillary disease or who have bulky lower mediastinal disease that places more breast tissue in the radiation field.

Gynaecological

Gynaecological cancers were not indicated for PT in any clinical indication list;[18-22] only one paper was found reporting on PT.[47] Van de Sande et al.[47] found favourable results with PT versus conventional X-rays for cervix and endometrium patients who had macroscopic para-aortic nodal involvement or isolated para-aortic recurrences. Intensity modulated proton therapy further reduced dose to all OARs and translated to a reduction in dose to the bone marrow decreasing haematological toxicities during treatment.[64]

Re-irradiation

Palliative re-irradiation was indicated in the USA and was a model-based indication for PT in Australia and New Zealand.[19] Previously irradiated head and neck patients where dose tolerances are at or close to tolerance were reported to benefit from PT.[38]

Other clinical decision-making tools

Several other approaches were used in the United States, UK, Europe and China. For prostate PT decision-making, informed decision-making[34] was a type of PT patient selection method used in the United States where clinicians explained all available treatment methods and patients had an option to choose treatment modality.[34] For head and neck re-irradiation in the United States and China, a multi-disciplinary team consensus was used, whereby a multi-disciplinary team convened to make treatment decisions.[38] In the UK, pre-chemotherapy characteristics were used to select lymphoma patients for PT versus X-rays.[7] In The Netherlands, an in-house hybrid clinical decision-making tool/dose comparison model was developed called the Proton Decision Support (PRODECIS) and was used to select head and neck patients for PT in three categories: dose metric, toxicity and cost-effectiveness.[16] Cost-effectiveness as a way to inform patient selection for management of breast, prostate, lung and liver cancer with PT was also reported by a team from the United States.[4,13]

Dose comparison methods

Fourteen dose comparison methods were identified: dosimetry/dose distribution comparison,[10] NTCP evaluation,[23] models incorporating NTCP, EUD and mean lung dose,[43] PRODECIS,[16] ReCompare,[54] knowledge-based DVH predictions,[3] a hypothesis-generating model,[45] Markov modelling,[65] influence diagram,[40] PST model,[36] predictive modelling via QuickMatch,[49] risk analysis/long-term outcomes,[44] simulation model[53] and a geometric knowledge-based method.[51] The most commonly reported tool was the NTCP model, followed by cost-effectiveness and dosimetry comparison. Dose comparison methods were applied to a variety of anatomical sites and for both paediatric and adult patients as shown in Table 4. Dose comparison methods were mostly used for patients receiving RT to the head and neck region.

Discussion

To our knowledge, this is the first paper that has collated the current global PT versus X-ray patient selection methods. The information reported captures the most recent PT clinical decision-making tools and dose comparison methods available, focussing on the interval of 1 January 2015 – August 4, 2020. This time interval captured the most recent X-ray and PT technology including IMRT, pencil beam scanning proton therapy and robust optimisation planning for proton therapy. However, as a majority of the papers captured were retrospective, it is likely that a proportion of papers reported on passive scanning rather than robustly optimised PT. Additionally, given the retrospective nature with sample sizes of one patient up to 1013 patients, larger prospective cohorts are required to further validate patient selection methods.

With the exception of paediatric patients and adult patients with base of skull, spinal or paraspinal tumours, there was uncertainty regarding other patient cohorts which may receive clinical benefit from PT and within which

Table 4. Dose comparison methods and their application to tumour sites (paediatric and adult cohorts combined)

Method	Tumour site: Brain	CNS	H&N	Breast	Lymphoma or Hodgkin lymphoma	Lung	Liver	Cervix or Endometrium	Prostate	Various
Dose Comparison	Munck[44] Adeberg[48] Stokkevag[67]		Jakobi[39] Wagenaar[50]	Maduro[30]	Tseng[32] Ntentas[7]	Chang[31] Teoh[46]		van de Sande[47]	Van Wijk[14]	Widder[15]
Model-based NTCP	Stokkevag[42] Munck[44]	Chaikh[43]	Lin[12] Blanchard[23]Brodin[25] Hansen[26] Kierkels[35] Tambas[36] Jakobi[39] Wagennar[50] Bijman[52] Quik[53] Scandurra[58]			McNamara[41] Teoh[46]	Mondlane[24]		Van Wijk[14]	Widder[15]
Markov modelling	Austin[61] Austin[56]			Austin[55] Mailhot[57]						
Risk Analysis/Long-term Outcomes					Tseng[32]					
ReCompare										Löck[54]
PRODECIS			Cheng[16]							
Knowledge-based DVH Predictions			Delaney[3]							
QuickMatch			Valdes[49]							
Hypothesis-generating model							Gandhi[45]			
Influence Diagram						Liao[33]				
Geometric Knowledge-based method	Hall[51]									
Simulation Model			Quik[53]							
New-PST model			Tambas[36]							
NTCP, EUD and mean lung dose						Chaikh[43]				

CNS, central nervous system; DVH, dose volume histogram; EUD, equivalent uniform dose; H&N, head and neck; NSCLC, non-small cell lung cancer; NTCP, normal tissue complication probability; PRODECIS, proton decision support; PST, pre-selection tool.

cohort PT is most cost-effective. Many studies have presented various clinical decision-making tools and dose comparison methods to facilitate this process; however, many methods were theoretical, require improvements or cannot be replicated in other countries due to differences in PT availability, resources and medical insurance schemes.

PT patient selection was clear and consistent for paediatric patients across all clinical indication lists. Few papers addressed clinical decision-making tools or dose comparison methods in paediatric populations due to decisive indication lists and certainty surrounding the benefit of PT in paediatric cancer cohorts.

PT patient selection was variable for adult patients. Dose comparison methods were applied to head and neck and brain sites most frequently, as the benefits of PT are theoretically maximised given the proximity of tumours to critical OARs in these sites.

Inherent relative biological effectiveness uncertainties are difficult to account for in any model and may affect patient selection. Many NTCP endpoints reported are only valid for X-rays and have not yet been validated in protons. Caution must be used when comparing PT plans between studies, as variations existed with some publications reporting on robustly optimised PT plans and others reporting on non-robustly optimised PT plans. Robust optimisation incorporates uncertainties (e.g. range uncertainty) into the planning optimiser, improving plan quality compared to conventional margin-based planning.[66] Plans created without robust optimisation could have been excluded to ensure that only the most current PT techniques were reported. Only 9 of the 19 countries with PT currently available were represented in the literature identified. This leaves a gap in knowledge related to PT patient selection methods used in about half of the countries that have PT available.

Limitations

Whilst this scoping review was completed rigorously, one aspect that warrants mentioning is inclusion of a third researcher, which would have helped to resolve conflicts in the literature screening process. Another limitation relates to study eligibility criteria and limits applied during database searches. It is possible that some studies (e.g. phantom studies or studies published in a language other than English) may have described PT decision-making tools, but were excluded from our database search and screening process.

Future Developments

With the rapid establishment of PT centres worldwide and accessibility to PT increasing, patient selection will simultaneously change. As PT becomes more widely available, indication lists will likely be expanded to include a more refined list of clinical indications. It is also possible that tools using a tiered or combined approach to patient selection for PT, such as those proposed by Brodin et al.[25] (combined – NTCP and Quality-Adjusted Life Years) and Cheng et al.[16] (three tiers – dose metric, toxicity and cost-effectiveness), are more likely to provide the most comprehensive evidence for which a technique is superior for a given patient, thus delivering truly personalised medicine. The emergence of long-term clinical outcomes of patients previously treated with PT will also guide future PT patient selection. One aspect that warrants future research is a comprehensive international survey of all operational PT centres which would provide greater insight into the current PT patient selection methods utilised globally and enable an overview of PT patient selection in the jurisdictions that may have been missed in this study.

In conclusion, with the exception of paediatric patients, this scoping review has shown there is currently no 'Gold Standard' to selecting patients for PT. There was a large amount of variability observed in the clinical decision-making tools and dose comparison methods in current use. It is expected that PT patient selection methods will continue to change with developments in proton and photon technology, the emergence of long-term PT data and the opening of more PT centres.

Conflicts of Interest

The authors have no conflicts to disclose.

Data Sharing Statement

All data analysed during this study is included in this article.

References

1. Baumann M, Krause M, Overgaard J, et al. Radiation oncology in the era of precision medicine. *Nat Rev Cancer* 2016; **16**: 234–49.
2. Particle Therapy Co-Operative Group. 2020, date accessed 15 March 2021 at https://www.ptcog.ch
3. Delaney AR, Dahele M, Tol JP, Kuijper IT, Slotman BJ, Verbakel W. Using a knowledge-based planning solution to select patients for proton therapy. *Radiother Oncol* 2017; **124**: 263–70.
4. Verma V, Mishra MV, Simone CB. Cost-effectiveness of proton beam therapy for oncologic management. *Int J Radiat Oncol Bio Phys* 2018; **101** (2 Supplement 1): E20.
5. Dwyer M. Defining the role of proton therapy in the optimal management of paediatric patients in Australia

and New Zealand. *J Med Imaging Radiat Oncol* 2016; **60**: 105–11.
6. Mangan S, Leech M. Proton therapy- the modality of choice for future radiation therapy management of Prostate Cancer? *Tech Innov Patient Support Radiat Oncol* 2019; **11**: 1–13.
7. Ntentas G, Dedeckova K, Andrlik M, et al. Clinical intensity modulated proton therapy for Hodgkin lymphoma: Which patients benefit the most? *Pract Radiat Oncol* 2019; **9**: 179–87.
8. Peeters A, Grutters JPC, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. *Radiother Oncol* 2010; **95**: 45–53.
9. Ahern V. Selecting patients for proton beam therapy. *J Med Radiat Sci* 2021; **68**: 2–3.
10. Weber DC, Habrand JL, Hoppe BS, et al. Proton therapy for pediatric malignancies: fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN. *Radiother Oncol* 2018; **128**: 44–55.
11. Austin A, Penfold S, Douglass M, Nguyen G. A radiobiological Markov simulation tool for aiding decision making in proton therapy referral. *Radiother Oncol* 2018; **127**(Supplement 1): S1079–S80.
12. Lin A, Rwigema JC, Lukens J, Swisher-McClure S, Langendijk J. Model-based clinical validation of proton therapy in head and neck cancer. *Radiother Oncol* 2018; **127**(Supplement 1): S179.
13. Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer* 2016; **122**: 1483–501.
14. Van Wijk Y, Roelofs E, Vanneste B, Walsh S, Lambin P. Comparing toxicity in IMRT and particle therapy of prostate cancer in a ROCOCO in silico trial. *Radiother Oncol* 2017; **123**(Supplement 1): S726–S7.
15. Widder J, Van Der Schaaf A, Lambin P, et al. The quest for evidence for proton therapy: model-based approach and precision medicine. *Int J Radiat Oncol Bio Phys* 2016; **95**: 30–6.
16. Cheng Q, Roelofs E, Ramaekers BL, et al. Development and evaluation of an online three-level proton vs photon decision support prototype for head and neck cancer - comparison of dose, toxicity and cost-effectiveness. *Radiother Oncol* 2016; **118**: 281–5.
17. Hwang EJ, Gorayski P, Le H, et al. Particle therapy toxicity outcomes: a systematic review. *J Med Imaging Radiat Oncol* 2020; **64**: 725–37.
18. Clinical Comissioning Policy: Proton Beam Therapy for Children, Teenagers and Young Adults in the treatment of malignant and non-malignant tumours: Version 1783: 2018. Accessed 29/07/20. Available from: https://www.england.nhs.uk/commissioning/spec-services/highly-spec-services/pbt/
19. The Royal Australian and New Zealand College of Radiologists. Position Paper on Paticle Therapy. Sydney, Australia the Royal Australian and New Zealand College of Radiologists; 2015.
20. Health Council of the Netherlands. Horizon Scanning Report. The Hague, Netherlands: Health Council of the Netherlands, 2009.
21. Alberta Health Service. Proton beam radiation therapy. Alberta Health Service; 2019.
22. Proton Beam Therapy (PBT). American Medical Association. Available from: https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf
23. Blanchard P, Wong AJ, Gunn GB, et al. Toward a model-based patient selection strategy for proton therapy: external validation of photon-derived normal tissue complication probability models in a head and neck proton therapy cohort. *Radiother Oncol* 2016; **121**: 381–6.
24. Mondlane G, Ureba A, Gubanski M, Lind PA, Siegbahn A. Estimation of the risk for radiation-induced liver disease following photon- or proton-beam radiosurgery of liver metastases. *Radiother Oncol* 2018; **13**: 206.
25. Brodin NP, Kabarriti R, Pankuch M, et al. A quantitative clinical decision-support strategy identifying which patients with oropharyngeal head and neck cancer may benefit the most from proton radiation therapy. *Int J Radiat Oncol Biol Phys* 2019; **104**: 540–52.
26. Hansen CR, Friborg J, Jensen K, et al. NTCP model validation method for DAHANCA patient selection of protons versus photons in head and neck cancer radiotherapy. *Acta Oncologica* 2019; **58**: 1410–5.
27. Proton therapy comparative planning. The Royal Adelaide Hospital, 2020. Available from: https://www.rah.sa.gov.au/health-professionals/clinical-services/medical/radiation-oncology
28. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005; **8**: 19–32.
29. Colquhoun HL, Levac D, O'Brien KK, et al. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol* 2014; **67**: 1291–4.
30. Maduro J. Future options: the potential role of proton irradiation. *Breast* 2019; **44**(Supplement 1): S10–S1.
31. Chang JY, Jabbour SK, De Ruysscher D, et al. Consensus statement on proton therapy in early-stage and locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2016; **95**: 505–16.
32. Tseng YD, Cutter DJ, Plastaras JP, et al. Evidence-based Review on the use of proton therapy in lymphoma from the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. *Int J Radiat Oncol Biol Phys* 2017; **99**: 825–42.

33. Liao Z, Gandhi SJ, Lin SH, Bradley J. Does proton therapy offer demonstrable clinical advantages for treating thoracic tumors? *Semin Radiat Oncol* 2018; **28**: 114–24.
34. Hoffman KE, Volk R, Chapin B, et al. Impact of multidisciplinary counseling on awareness of prostate cancer treatment options. *Int J Radiat Oncol Bio Phys* 2019; **105**(1 Supplement): E442.
35. Kierkels RGJ, Fredriksson A, Both S, Langendijk JA, Scandurra D, Korevaar EW. Automated proton planning by mimicking the reference photon dose for patient selection. *Radiother Oncol* 2018; **127**(Supplement 1): S109–10.
36. Tambas M, van der Laan HP, Hoek AVD, et al. Preselection tool for the model-based selection of head and neck cancer patients for proton therapy. *Int J Radiat Oncol Bio Phys* 2019; **105**(1 Supplement): E384.
37. Mondlane G, Ureba A, Gubanski M, Lind PA, Siegbahn A. Estimation of risk of normal-tissue toxicity following gastric cancer radiotherapy with photon- or scanned proton-beams. *Anticancer Res* 2018; **38**: 2619–25.
38. Fan D, Fan M, Wang H, et al. Last-line local treatment with the quad shot regimen for previously irradiated head and neck cancers. *Int J Radiat Oncol Bio Phys* 2020; **106**: 1179.
39. Jakobi A, Bandurska-Luque A, Stutzer K, et al. Identification of patient benefit from proton therapy for advanced head and neck cancer patients based on individual and subgroup normal tissue complication probability analysis. *Int J Radiat Oncol Biol Phys* 2015; **92**: 1165–74.
40. Smith WP, Richard PJ, Zeng J, Apisarnthanarax S, Rengan R, Phillips MH. Decision analytic modeling for the economic analysis of proton radiotherapy for non-small cell lung cancer. *Transl Lung Cancer Res* 2018; **7**: 122–33.
41. McNamara AL, Hall DC, Shusharina N, et al. Perspectives on the model-based approach to proton therapy trials: a retrospective study of a lung cancer randomized trial. *Radiother Oncol* 2020; **147**: 8–14.
42. Stokkevag CH, Indelicato DJ, Herfarth K, et al. Normal tissue complication probability models in plan evaluation of children with brain tumors referred to proton therapy. *Acta Oncologica* 2019; **58**: 1416–22.
43. Chaikh A, Calugaru V, Bondiau PY, Thariat J, Balosso J. Impact of the NTCP modeling on medical decision to select eligible patient for proton therapy: the usefulness of EUD as an indicator to rank modern photon vs proton treatment plans. *Int J Radiat Biol* 2018; **94**: 789–97.
44. Munck af Rosenschold P, Engelholm SA, Brodin PN, et al. A Retrospective evaluation of the benefit of referring pediatric cancer patients to an external proton therapy center. *Pediatr Blood Cancer* 2016; **63**: 262–9.
45. Gandhi SJ, Liang X, Ding X, et al. Clinical decision tool for optimal delivery of liver stereotactic body radiation therapy: photons versus protons. *Pract Radiat Oncol* 2015; **5**: 209–18.
46. Teoh S, Fiorini F, George B, Vallis KA, Van den Heuvel F. Proton vs photon: a model-based approach to patient selection for reduction of cardiac toxicity in locally advanced lung cancer. *Radiother Oncol* 2019; **152**: 151–62.
47. van de Sande MAE, Creutzberg CL, van de Water S, Sharfo AW, Hoogeman MS. Which cervical and endometrial cancer patients will benefit most from intensity-modulated proton therapy? *Radiother Oncol* 2016; **120**: 397–403.
48. Adeberg S, Harrabi S, Bougatf N, et al. Dosimetric comparison based on intracranial location of intensity modulated proton therapy (IMPT), volumetric arc therapy (VMAT), and 3D-conformal radiotherapy (3D-CRT) in primary brain tumor patients. *Oncol Res Treat* 2018; **41** (Supplement 1): 152.
49. Valdes G, Wojtowicz L, Pattison AJ, et al. Machine learning-based enables data-driven radiotherapy treatment planning decision support. *Radiother Oncol* 2017; **123** (Supplement 1): S127–S8.
50. Wagenaar D, Kierkels RGJ, Free J, Langendijk JA, Korevaar EW. Robust optimization of VMAT in head and neck patients. *Radiother Oncol* 2017; **123**(Supplement 1): S234–S5.
51. Hall DCDP, Trofimov AVPD, Winey BAPD, Liebsch NJMDPD, Paganetti HPD. Predicting patient-specific dosimetric benefits of proton therapy for skull-base tumors using a geometric knowledge-based method. *Int J Radiat Oncol Biol Phys* 2017; **97**: 1087–94.
52. Bijman RG, Breedveld S, Arts T, et al. Impact of model and dose uncertainty on model-based selection of oropharyngeal cancer patients for proton therapy. *Acta Oncol* 2017; **56**: 1444–50.
53. Quik EH, Feenstra TL, Postmus D, et al. Individual patient information to select patients for different radiation techniques. *Eur J Cancer* 2016; **62**: 18–27.
54. Löck S, Roth K, Skripcak T, et al. Implementation of a software for REmote COMparison of PARticlE and photon treatment plans: ReCompare. *Z Med Phys* 2015; **25**: 287–94.
55. Austin AM, Douglass MJJ, Nguyen GT, et al. Individualised selection of left-sided breast cancer patients for proton therapy based on cost-effectiveness. *J Med Radiat Sci* 2020; **68**: 44–51.
56. Austin AM, Douglass MJJ, Nguyen GT, Penfold SN. Patient selection for proton therapy: a radiobiological fuzzy Markov model incorporating robust plan analysis. *Australas Phys Eng Sci Med* 2020; **43**: 493–503.
57. Mailhot Vega RB, Ishaq O, Raldow A, et al. Establishing cost-effective allocation of proton therapy for breast irradiation. *Int J Radiat Oncol Bio Phys* 2016; **95**: 11–8.

58. Scandurra D. Advanced selection procedures for proton therapy in head and neck cancer patients. *Radiother Oncol* 2018; **127**(Supplement 1): S179–S80.
59. Weber DC, Abrunhosa-Branquinho A, Bolsi A, et al. Profile of European proton and carbon ion therapy centers assessed by the EORTC facility questionnaire. *Radiother Oncol* 2017; **124**: 185–9.
60. Adeberg S, Harrabi S, Bougatf N, et al. Dosimetric comparison of proton RT with standard of care photon RT techniques in CNS tumors. *Radiother Oncol* 2018; **127** (Supplement 1): S677.
61. Austin AM, Penfold SN, Douglass MJJ, Nguyen GT. A radiobiological Markov simulation tool for aiding decision making in proton therapy referral. *Australas Phys Eng Sci Med* 2018; **41**(1): 297.
62. Valdes G, Simone CB, Chen J, et al. Clinical decision support of radiotherapy treatment planning: a data-driven machine learning strategy for patient-specific dosimetric decision making. *Radiother Oncol* 2017; **125**: 392–7.
63. Smith B, Gelover E, Moignier A, et al. Technical Note: A treatment plan comparison between dynamic collimation and a fixed aperture during spot scanning proton therapy for brain treatment. *Med Phys* 2016; **43**: 4693–9.
64. van de Schoot AJAJ, de Boer P, Visser J, Stalpers LJA, Rasch CRN, Bel A. Dosimetric advantages of a clinical daily adaptive plan selection strategy compared with a non-adaptive strategy in cervical cancer radiation therapy. *Acta Oncologica* 2017; **56**: 667–74.
65. Mailhot Vega R, Formenti SC, MacDonald S. Cost-effective analysis of proton therapy for breast irradiation. *Int J Radiat Oncol Bio Phys* 2015; **93**: S91.
66. Unkelbach J, Paganetti H. Robust proton treatment planning: physical and biological optimization. *Semin Radiat Oncol* 2018; **28**: 88–96.
67. Stokkevag CH, Fukahori M, Nomiya T, et al. Modelling of organ-specific radiation-induced secondary cancer risks following particle therapy. *Radiother Oncol* 2016; **120**: 300–6.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 Search strategy used in scoping review*.