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.5,6,7 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.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.7–36

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 publicly 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), 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, five were government or medical college clinical indication lists, eight were literature reviews, 28 were retrospective studies, 22 prospective studies. One publication was a case-control study, and one was an expert opinion. 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. Ten countries who currently have PT operational including Austria, Belgium, Czech Republic, India, Italy, Japan,
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), United Kingdom (UK), Canada, The Netherlands, Australia and New Zealand. 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), 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                   | - 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                                                            |
| Diagnosis/clinical indications              |                                                                             |                                                                          |                                                                             |
| list18-22                                   | - Consensus-based list of diagnoses eligible for PT                         | - Assists department workload                                           | - May exclude patients who could benefit from PT                            |
| Pre-chemotherapy characteristics7           | - Patient is selected based on chemotherapy characteristics                | NR                                                                      | - Sample size of the study was low (n = 21)                                 |
| Multi-disciplinary team consensus38         | - A multi-disciplinary team convenes to make treatment decisions            | - Personalisation                                                       |                                                                             |
| Cost-effectiveness13,59                     | - 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 / Dosimetry60          | - Comparison of proton and X-ray computed dose distributions                | - Cost-effective                                                        | - Time intensive as multiple plans need to be generated                     |
| NTCP12,26,37,43,52                          | - NTCPs are compared between plans                                          | - Decreased resources                                                    | - Uncertainty in comparison of non-robustly optimised proton plans           |
| Knowledge-based DVH predictions3            | - Organ toxicity endpoints compared between plans                           | - Individualised                                                         | - RBE uncertainties                                                         |
| Influence diagram40                         | - 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                                              | - Inter-patient variation in radio-sensitivity                              |
| Predictive modelling via QuickMatch49       | - Plan prediction software (QuickMatch) predicted radiation doses to PTVs and OARs | - Objective method                                                      | - Time intensive                                                            |
| ReCompare54                                 | - Uses client-server-based software for conventional radiation therapy centres to have plan comparisons completed with PT centres | - Results in quality improvement                                        | - Novel technique, requires further validation                              |
| Simulation model53                          | - A model developed for tracking individual patient’s status of NTCP and GTV | - Improved workflow                                                     | - Time intensive                                                            |
| Geometric knowledge-based method51          | - Computers use the geometric arrangement of tumour and organs to compare plans | - Computationally efficient                                              | - Created proton plans cannot be used for treatment due to Hounsfield unit conversions and differences in patient positioning |
|                                             |                                                                             | - Less resource-intensive                                               | - HRQoL values were missing for few complication strategies                 |
|                                             |                                                                             | - Can be used for patient selection assessment by insurance companies    | - RBE uncertainties                                                         |

(Continued)
Dose comparison methods

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

Adults

Clinical decision-making

Within the adult population, six different clinical decision-making tools were identified: Proton Decision...
Support (PRODECIS),\textsuperscript{16} informed decision-making,\textsuperscript{34} clinical indications list,\textsuperscript{6} pre-chemotherapy characteristics,\textsuperscript{7} cost-effectiveness\textsuperscript{4} and multi-disciplinary team consensus.\textsuperscript{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.\textsuperscript{18–22} Variability was seen for all other tumour sites as well as for including re-irradiation.

Table 2. Clinical indications for proton therapy in paediatric patients

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

Brain, skull base, ocular and head and neck tumours

PT for brain indications was variable in adult cohorts. Adeberg et al.\textsuperscript{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.\textsuperscript{16–22} 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.\textsuperscript{5,42} PT was also indicated for ocular tumours in the United States,\textsuperscript{22} Canada,\textsuperscript{21} Australia and New Zealand.\textsuperscript{19} Verma et al.\textsuperscript{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,\textsuperscript{21} nasopharyngeal carcinoma in the UK\textsuperscript{18} and advanced and/or unresectable head and neck cancers in the United States.\textsuperscript{22} PT may be cost-effective for some patients with head and neck cancers.\textsuperscript{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
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\(^{37}\) 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

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**Table 3. Clinical indications for proton therapy in adults**

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

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.
indications and cost-effectiveness of PT. One paper reported that PT for prostate cancer was not cost-effective, whereas cost-effectiveness may be achieved for younger and favourable-risk prostate cancer patients.

**Lymphoma**

Variability in PT for lymphoma patients existed; Canada indicates lymphoma for PT, the Netherlands indicates PT for lymphoma in patients less than 30 years old, and lymphoma is a model-based indication in the United States. Ntentas et al. 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. 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; only one paper was found reporting on PT. Van de Sande et al. 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.

**Re-irradiation**

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

**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 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. 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. In the UK, pre-chemotherapy characteristics were used to select lymphoma patients for PT versus X-rays. 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. 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.

**Dose comparison methods**

Fourteen dose comparison methods were identified: dosimetry/dose distribution comparison, NTCP evaluation, models incorporating NTCP, EUD and mean lung dose, PRODECIS, ReCompare, knowledge-based DVH predictions, a hypothesis-generating model, Markov modelling, influence diagram, PST model, predictive modelling via QuickMatch, risk analysis/long-term outcomes, simulation model and a geometric knowledge-based method. 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          | Lymphoma or Hodgkin lymphoma | Lung | Liver | Cervix or Endometrium | Prostate | Various |
|-----------------------------|----------------------|-------------------------------|------|-------|------------------------|----------|---------|
| Dose Comparison Munck       | Brain                | H&N                           |      |       |                        |          |         |
| Adeberg                     |                      |                               |      |       |                        |          |         |
| Stokkevag                  |                      |                               |      |       |                        |          |         |
| vander Sande                |                      |                               |      |       |                        |          |         |
| Van Wijk                    |                      |                               |      |       |                        |          |         |
| Widder                      |                      |                               |      |       |                        |          |         |
| Model-based NTCP Stokkevag |                      |                               |      |       |                        |          |         |
| Chaikh                      |                      |                               |      |       |                        |          |         |
| Munck                       |                      |                               |      |       |                        |          |         |
| Lin                         |                      |                               |      |       |                        |          |         |
| Blanchard                   |                      |                               |      |       |                        |          |         |
| Brodin                      |                      |                               |      |       |                        |          |         |
| Hansen                      |                      |                               |      |       |                        |          |         |
| Jakobi                      |                      |                               |      |       |                        |          |         |
| Wagenaar                   |                      |                               |      |       |                        |          |         |
| Tseng                       |                      |                               |      |       |                        |          |         |
| Chang                       |                      |                               |      |       |                        |          |         |
| Teoh                        |                      |                               |      |       |                        |          |         |
| McNamara                    |                      |                               |      |       |                        |          |         |
| Mondlane                    |                      |                               |      |       |                        |          |         |
| Markov modelling Austin     |                      |                               |      |       |                        |          |         |
| Austin                      |                      |                               |      |       |                        |          |         |
| Risk Analysis/Long-term Outcomes |                |                               |      |       |                        |          |         |
| ReCompare                   |                      |                               |      |       |                        |          |         |
| PRODECIS                    |                      |                               |      |       |                        |          |         |
| Knowledge-based DVH Predictions |                |                               |      |       |                        |          |         |
| QuickMatch                  |                      |                               |      |       |                        |          |         |
| Hypothesis-generating model |                      |                               |      |       |                        |          |         |
| Influence Diagram           |                      |                               |      |       |                        |          |         |
| Geometric Knowledge-based method |                |                               |      |       |                        |          |         |
| Simulation Model            |                      |                               |      |       |                        |          |         |
| New-PST model               |                      |                               |      |       |                        |          |         |
| NTCP, EUD and mean lung dose |                      |                               |      |       |                        |          |         |

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. 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. (combined – NTCP and Quality-Adjusted Life Years) and Cheng et al. (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.

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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*. 

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*This document contains a list of references and possibly other supporting information. The references are formatted according to a specific citation style.*

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