The Promise of Proton Beam Therapy for Oesophageal Cancer: A Systematic Review of Dosimetric and Clinical Outcomes

Owen Nicholas MD FRCR[1,2], Susan Prosser MSc[1], Hanna Rahbek Mortensen MD PhD[3], Ganesh Radhakrishna MD FRCR[4], Maria A. Hawkins MD FRCR[5], Sarah H. Gwynne MD[1,2]

South West Wales Cancer Centre, Swansea, United Kingdom[1]; Swansea University Medical School[2], Swansea, United Kingdom; The Danish Centre for Particle Therapy, Aarhus University Hospital[3], Aarhus, Denmark; The Christie NHS Foundation Trust, Manchester, United Kingdom[4]; University College Hospital NHS Foundation Trust, London, United Kingdom[5]

Corresponding author:
Dr Owen Nicholas MD FRCR (owen.nicholas@wales.nhs.uk) South West Wales Cancer Centre, Singleton Hospital, Sketty Lane, Swansea, United Kingdom SA2 8QA.

Conflict of interest:
All authors have nothing to disclose.

Acknowledgments: Owen Nicholas is partially funded by the South West Wales Cancer Fund (charity no. 1122805). Maria A. Hawkins is funded by MRC grant (ref. MC_PC_12001/2).

Purpose:

Due to its physical advantages over photon radiotherapy (RT), proton beam therapy (PBT) has the potential to improve outcomes from oesophageal cancer. However, for many tumour sites, high quality evidence supporting PBT use is limited. We perform a systematic review of published literature of PBT in oesophageal cancer to ascertain potential benefits of this technology and to gauge the current state-of-the-art. We consider if further evaluation of this technology in oesophageal cancer is desirable.

Materials and Methods:

A systematic literature search of Medline, Embase, Cochrane Library and Web of Science using structured search terms was performed. Inclusion criteria included non-metastatic cancer, full articles and English language studies only. Articles deliberating technical aspects of PBT planning or delivery were excluded to maintain a clinical focus. Studies were divided into 2 sections; dosimetric and clinical studies; and qualitatively synthesised.

Results:

467 records were screened with 32 included for final qualitative synthesis. This included two prospective studies with the rest based on retrospective data. There is heterogeneity in treatment protocols including treatment intent (neoadjuvant or definitive), dose, fractionation and chemotherapy used. Compared to photon RT, PBT appears to reduce dose to organs-at-risk, especially lung and heart, although not for all reported parameters. Toxicity outcomes, including post-operative complications, are reduced compared to photon RT. Survival outcomes are reported to be at least comparable to photon RT.

Conclusion

There is a paucity of high-quality evidence supporting PBT use in oesophageal cancer. Wide variation in intent and treatment protocols means the role and 'gold-standard' treatment protocol is yet to be defined. Current literature suggests significant benefit in terms of toxicity reduction, especially in the post-operative period, with comparable survival outcomes. PBT in oesophageal cancer holds significant promise for improving patient outcomes but needs robust systematic evaluation in prospective studies.

Introduction

Oesophageal cancer is the 6th most common cause of cancer mortality worldwide, accounting for over 508,000 deaths in 2018.[1] Despite significant progress over recent decades, long-term outcomes remain disappointing with 10 year survival rates of around 12%. [2] Cancer Research UK, the world's largest independent funder of cancer research, has recognised this ongoing unmet clinical need with oesophageal cancer remaining one of four priority tumour sites in their updated 2017 research strategy.[3, 4]

While surgery remains the mainstay of curative treatment, chemoradiotherapy (CRT) has emerged as an invaluable treatment modality for localised oesophageal cancer in both the neoadjuvant (NA) and definitive setting. In the NA CRT setting, the phase 3 CROSS trial reported a doubling of overall survival compared to surgery alone making NA CRT an international standard of care. [5] However, tri-modality treatment is associated with significant toxicities. A recent prospective surgical database, of which 46.1% received NACRT, reported a 59% rate of post-operative complications including significant rates of pneumonia (14.6%) and atrial dysrhythmias (14.5%) [6]. Concerns over toxicities have been cited as reasons for the low usage of NA CRT in the UK where NA or peri-operative chemotherapy is commonly used [7, 8]. Of note, the recently published FlOT4 study of perioperative FlOT chemotherapy resulted in post-operative complications rates of around 50%. [9] For definitive CRT, trial data suggests slightly inferior but comparable survival rates to published surgical outcomes in a patient group largely unfit for surgery making CRT a viable alternative for curative treatment. [10-12] For squamous cell cancers (SCC), definitive CRT is increasingly considered a standard of care, on par with surgical resection. [13, 14]

Over the past decade, technological advances in radiotherapy have gradually transformed the treatment of oesophageal cancer. While many of the reported large randomised controlled trials (RCTs) utilised 2D or 3D conformal radiotherapy (2D/3DCRT) [5, 10, 11], in clinical practice today this has increasingly been superseded by more advanced techniques such as IMRT/VMAT.[15] The use of

these modern conformal techniques widens the therapeutic window, allowing a reduction in dose to organs at risk (OARs) while maintaining dose to the target volume. This potentially leads to improved survival, possibly due to a reduction in non-cancer related mortality.[16, 17] Increased dose modulation also allows dose escalation in an attempt to improve tumour control, the merits of which are uncertain; as seen in the negative results of the INT0123 and ARTDECO studies; but remains under evaluation in the UK SCOPE 2 trial. [18-21]

The technological evolution continues with the advent of particle beam therapy, of which proton beam therapy (PBT) is currently the most widely available. PBT's Bragg peak results in a sharp dose fall-off at the distal edge of the beam thereby eliminating the impact of the "exit" dose from photon therapy. [22] Relative biological effects (RBE) of PBT may contribute to greater tumour control albeit with potentially higher rates of normal tissue complications. [23] Whilst this technology has been present for several decades, the number of centres delivering PBT has substantially increased in recent years, widening access to this treatment modality for patients across the world.[24] For certain indications such as paediatric cancers and skull base tumours, PBT is now an accepted standard form of treatment and are recommended in international guidelines. [25, 26] However, for most adult indications the evidence base is substantially less robust. [27]

In Europe, the drive to systematically assess PBT, in terms of clinical efficacy and cost-effectiveness, is gaining momentum. The European Organisation for Research and Treatment of Cancer (EORTC) has recently published a report highlighting the evaluation of PBT in tumour sites which may benefit from the improved therapeutic ratio as a research priority.[28] The UK's National Cancer Research Institute (NCRI)-funded Clinical and Translational Radiotherapy Group (CTRAD) has established a PBT clinical trial strategy group with the aim of delivering high quality clinical trials of PBT, the first of which, the TORPEdO study, commenced recruitment in early 2020. [29, 30] The UK's National Health Service (NHS) PBT service [31], once fully ramped up, will have a combined treatment capacity of approximately 1500 patients/year, deliberately exceeding current patient demand based on UK

criteria. In alignment with wider European strategy, the NHS has made systematic evaluation of PBT a central objective, allocating nearly 50% of treatment capacity for research. [30, 31]

Oesophageal cancer is a tumour site that may benefit from PBT due its location in the central mediastinum and proximity to critical OARs. Most oesophageal cancers occur in the mid or distal third oesophagus, within close proximity to the heart, lung, liver and spleen. PBT allows maintenance or escalation of dose to the target volume while simultaneously reducing dose to these OARs. Dosimetric superiority potentially translates into improved toxicity and survival outcomes. These links are seen in tumours near the mediastinum, such as in lung cancer where dose to lung is shown to correlate with pneumonitis rates and heart dose has been found to be a prognostic factor for long-term survival.[32, 33] For breast cancer, an increase of 1Gy mean heart dose results in a 7.4% increase rate of major coronary events. [34] In oesophageal cancer, the links are less established but emerging data suggests a similar relationship between dosimetric and clinical outcomes. For example, Wang et al. showed that mean lung dose correlated with post-oesophagectomy complication rates [35]while Takeuchi et al. showed that mean heart dose correlated with rates of symptomatic pericardial effusions following radiotherapy for oesophageal cancer.[36] It is clear that PBT, with its physical advantages, may meaningfully contribute to improving outcomes in oesophageal cancer. This review aims to assess the current evidence base that supports or refutes this hypothesis.

Aims and objectives

This review of current literature aims to assess and summarise potential advantages of PBT over standard RT techniques for patients with localised oesophageal cancer. To ensure a clinical focus, this analysis assesses relevant dosimetric parameters that may result in improved clinical outcomes, like dose to critical OARs such as the heart and lung and target volume coverage. In addition, it summarises any reported clinical endpoints such as toxicity rates, local control rates and survival outcomes. The overall objective of this study is to give an up-to-date and comprehensive overview of the use of PBT in oesophageal cancer, its potential benefits and highlight current issues

surrounding its use. More importantly, this review assesses if further evaluation of PBT in oesophageal cancer, preferably in the context of robust RCTs, is warranted.

PICO (Population, Intervention, Comparison, Outcome) Questions

1. In patients with non-metastatic oesophageal cancer, does PBT offer dosimetric advantages over photon radiotherapy?
2. In patients with non-metastatic oesophageal cancer, does PBT confer any improvements in measurable clinical outcomes compared to photon radiotherapy?

Outcomes and Measures

Co-Primary outcome

- Proton beam therapy gives a statistically significant ($p<0.05$) reduction in dose parameters to OARs (e.g. lung and heart) while maintaining an equal or comparable dose to target volume.
- Proton beam therapy has evidence of clinical benefit measured by endpoints such as overall survival, progression free survival and toxicity endpoints.

Secondary outcomes

- Descriptions of treatment protocols of PBT in oesophageal cancer including intent/dose/fractionation/chemotherapy type.
- Current techniques used to deliver PBT to oesophagus (e.g. pencil beam scanning, passive-scattering)
- Key volumetric descriptors used to assess proton beam therapy for oesophageal cancer

Eligibility Criteria

Inclusion Criteria

- Full text articles only
- Non-metastatic oesophageal cancer
- All patients 18 or over
- Published after 2010

Exclusion criteria

- Articles focussing on the technical aspects of PBT planning and delivery
- Articles focussing on quality of life questionnaire data
- Articles focussing on health economics aspects of PBT
- Review articles
- Non-full text articles
- Non-English
- Studies with non-oesophageal cancer patients
- Studies with non-localised oesophageal cancer patients
- Studies with fewer than 10 patients
- Studies with multiple publications on the same cohort (unless reporting different endpoints)
- Studies using PBT for re-irradiation

Study types for sub-analysis

Dosimetric studies

Dosimetric studies; experimental (planning study), prospective or retrospective clinical data

Clinical studies

Prospective and retrospective studies reporting clinical outcomes with PBT in oesophageal cancer

Table 1 - PICO Question and Full Eligibility Criteria

Methods

Search Strategy

A systematic review was performed using structured search terms following the Preferred Report Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic literature search was performed using Medline, Embase, Cochrane Library and Web of Science. The initial search was performed on 17th March 2020 and last performed on 17th December 2020. All databases were searched from 2010 to present to reflect current available technology. Thesaurus and natural language terms around the concepts of 'cancer of the oesophagus', 'proton beam therapy', and 'proton planning' were identified for each database. Searches were performed on text wording rather than title or abstract alone. Full reference lists of studies selected for inclusion from the initial searches were reviewed for additional manuscripts of interest (backward chaining). Citation checks of the final selected studies were also performed on Web of Science and Google Scholar on 17th December 2020. Full search methodology including search terms for each database and a PRISMA checklist are included in the appendix.

Eligibility criteria

Eligible studies were English language studies for non-metastatic oesophageal cancer, involving patients over the age of 18. Studies that reported outcomes for re-irradiation or metastases including oligo-metastases were excluded. Studies relating to the technical aspects of proton beam therapy planning and delivery e.g. motion management, planning optimisation, were deliberately excluded in order to maintain a clinical focus, as were studies assessing the health economic implications of this technology. Full objectives including PICOs question, outcomes and eligibility criteria are detailed in table 1.

Study selection

Duplicates and conference abstracts were removed, and remaining articles were assessed for eligibility by two independent reviewers (ON, SG). A total of 256 full-text articles were assessed for eligibility, with 32 articles selected for inclusion in final analysis. See PRISMA flow diagram (figure 1) for full details. The analysis is divided into two sections; dosimetric studies and clinical studies. The

first section considers all relevant dosimetric studies, including studies which included comparison to standard photon techniques such as IMRT/VMAT and 3D-CRT. The second section considers reported clinical outcomes including survival and toxicity endpoints. Five studies included both dosimetric data and clinical outcome data. For these studies, dosimetric outcomes are detailed in the dosimetric studies section (see table 2) and clinical outcomes are detailed in the clinical studies section (see table 3).

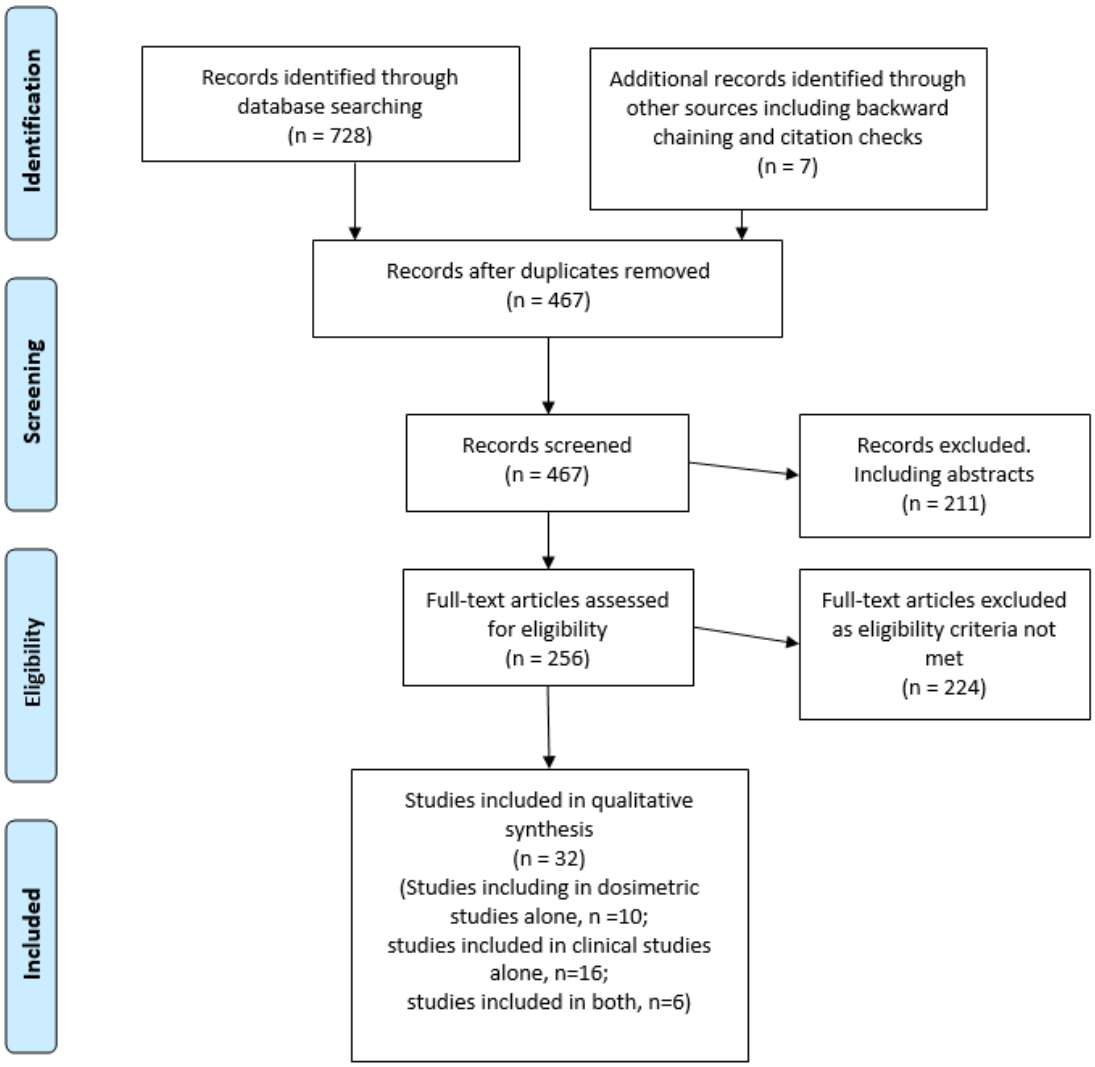

Figure 1: PRISMA Flow Diagram

Results

Table 2: Dosimetric Studies

Ref.	Study Design	No. of patients (n) and tumour type	RT intent/protocol	PBT technique	Comparison	Results	Notes
Xi et al., 2017[37]	Retrospective, Single centre (MDACC)	n = 343 (PBT, n=132; IMRT n=211) Mostly distal AC	Definitive 50.4Gy/28# with chemotherapy	PS/PBS	IMRT	PBT superior: Lung – Mean, V5, V10, V20; Heart – Mean, V30. No difference: PTV coverage; Heart V40	Clinical outcome data in Table 3
Shiraishi et al., 2017[38]	Retrospective, Single centre (MDACC)	n = 727 (PBT, n=250; IMRT, n=477) Mostly distal AC	Definitive/NA 50.4Gy/28# mostly with chemotherapy	Mostly PS (PBS, n = 13)	IMRT PS vs PBS	*PBT vs IMRT* PBT superior for all cardiac substructures except RCA -V30, V40; LCX -V30, V40 *PBS vs PS* PBS superior: Whole heart - V20, V30, V40; RA – mean, V5, V10, V20, V30, V40; LA – V30, V40; LMC- mean, V20, V30, V40; LCX – V10, V20, V30, V40; No difference: RV/LV/LAD/RCA.	
Welsh et al., 2011[39]	Retrospective, Single centre (MDACC)	n=10 Distal tumours	Definitive 50.4Gy/28 # (PTV) 65.8Gy/28 # (GTV) with chemotherapy	PBS	IMRT vs 3 PBT beam arrangements	*IMRT vs AP/PA* PBT superior: Lung – Mean, V5, V10, V20; Spinal cord. No difference: Heart; Liver.	

						IMRT vs LPO/RPO PBT superior: Lung – mean, V5, V10; Heart – mean, V10, V20, V20, V30; Liver – mean. No difference: lung V20; Spinal Cord. *IMRT vs AP/LPO/RPO* PBT superior: Lung – mean, V5, V10, V20; Heart – Mean, V10, V20, V30; Liver; spinal cord. Comparable coverage of GTV/PTV for all beam arrangements	
Jingya Wang et al., 2015[40]	Retrospective, Single centre (MDACC)	n = 55 Mostly distal tumours	Definitive/ NA 50.4/28# with chemotherapy	PS	IMRT	PBT superior: Lung – Mean, V5, V10, V20; Heart –V10, V20, V30, V40; Cord (Dmax); Liver - mean. IMRT superior: Lung - V40, V45, V50. No difference: Mean heart dose.	Distance of PTV to carina and percentage of uninvolved heart inversely correlated to mean lung and heart dose respectively
Wang et al. 2020 [41]	Retrospective analysis of G3+ Cardiac events, Single centre (MDACC)	n=479 (PBT=159; IMRT, n=320)	Definitive/NA 41.4Gy/23# - 50.4Gy/28# With chemo	PS/PBS	IMRT	PBT superior: Heart - V5, V30, Mean Cardiac dose parameters associated to G3+ Cardiac events	Clinical outcomes in Table 3

Prayongrat, et al., 2017[42]	Retrospective, Single centre (MDACC)	n = 19 SCC and AC	Definitive/NA 41.4-50.4Gy/23-28# With chemotherapy	PBS	-	Selected results: Mean Lung dose – 4.94Gy (±2.31); Lung V20 - 9.45% (± 4.94); Mean Heart dose - 7.86Gy (±5.04); Acceptable PTV coverage.	Clinical outcome data in Table 3
Hirano et al., 2018[43]	Retrospective, Single Centre (NCCJ)	n=27 SCC only	Definitive 60Gy/30# with chemotherapy	PBS	3DCRT IMRT	*PBT vs 3DCRT* PBT superior: Lung – Mean, V5, V20; Heart - V10, V20, V30, V40; Spinal cord (max dose); Conformity index (CI)*. No difference: Lung V10, V15. *PBT vs IMRT* PBT superior: Lung - Mean, V5, V10, V20; Heart - Mean, V20, V30, V40; CI. No difference: Spinal cord (max dose). No correlation between toxicities and dosimetric parameters	CI determined as the volume of the 90% prescription isodose surface divided by PTV
Ling et al.,2014 [44]	Retrospective, Single Centre (LLUMC)	n = 10 AC only	NA 50.4Gy/28#, no chemotherapy information	PS	3DCRT IMRT	*PBT vs IMRT* PBT superior: Lung – Mean, V5, V10, V15; Heart – mean, V25, V30, V40, V50, LAD, LV, pericardium; Other – Liver, Spinal cord, stomach V50. No difference: Lung V20, V30, V40; stomach V20; CI; Uniformity index (UI); homogeneity index (HI)	

						PBT vs 3DCRT PBT superior: Lung – V5, V50; Heart – Mean, V25, V30, V40, V50, LAD LV, Pericardium; Other – liver, spinal cord; UI, HI. No difference: CI	
Liu et al., 2019[45]	Retrospective, Single centre (Mayo)	n=35 (PBT, n=19; IMRT, n=16)	Definitive/NA 50.4Gy/28# No chemotherapy information	PBS	VMAT	PBT superior: Lung – Mean, V5; Heart – mean, V30; Liver – Mean, V20. No difference: Lung V20; Heart- V30, V40; liver -V30; spinal cord; kidney; stomach.	Utilised small-spot IMPT VMAT resulted in more robust coverage of CTV
Makishima et al., 2015[46]	Retrospective, Single Centre (PMRC/UoT)	n=44 SCC only	Definitive 60Gy (median) with chemotherapy	PS	3DCRT	PBT superior: Lung – Mean, V5, V10, V20; Heart -V30, 40, 50.	Unmatched baseline characteristics with comparison group Clinical outcome data in Table 3
Macomber et al., 2018[47]	Retrospective, Single centre (SCCA/UoW)	n=55 (PBT, n= 18; IMRT, n=21; 3DCRT, n=16) Mostly distal AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT 3DCRT	PBT superior: Heart – Mean, V5, V40. No difference: Heart V50. No correlation between dose and clinical outcomes (see table 3).	Clinical outcome data in Table 3

Zeng et al., 2016[48]	Retrospective, Single centre (SCCA/UoW)	n = 13 Mid and distal tumours, SCC/AC	NA 50.4Gy/28# with chemotherapy	PS/PBS	PBT beam arrangements: PA vs AP/PA PA vs PA/LPO AP/PA vs PA/LPO	PA vs AP/PA: PA has lower heart dose (except V40), comparable lung dose PA vs PA/LPO: PA has lower lung dose, other parameters comparable. AP/PA vs PA/LPO: AP/PA has lower lung dose, higher heart dose. PA - highest cord doses but all within tolerance	Mid-oesophageal tumours excluded from dosimetric comparison Clinical outcome data in table 3
Feng et al. 2020 [49]	Planning Study	n=20 Distal tumours only	50Gy/25#	PBS	2 Superior-Inferior (S-I) direction posterior oblique beams (couch 270°) 2 Right-Left (R-L) direction posterior oblique beams (couch 180°)	*S-I vs R-L beam arrangements:* S-I superior: Lung – V5, V30 Liver -Dmean, NTCP endpoints R-L superior: Cord Dmax CTV hot-spot control Comparable plan robustness for S-I and R-L When interplay considered, S-I superior for heart Dmean and V30, lung Dmean and V5Gy, Liver Dmean. Higher Cord Dmax	Matched tumour volume characteristics
Celik et al. 2020 [50]	Planning Study	n=20 GOJ tumours (Sievert I and II)	NA 41.4Gy/23#	PBS	PBT 2 Field(2F) PBT 3 Field(3F) VMAT	Selected results (*VMAT vs 2F vs 3F):* Mean lung dose - 8.6±2.9Gy vs 3.2±1.5 Gy vs 2.9 ± 1.2Gy Mean heart dose - 9.9±1.9Gy vs 3.7 ± 1.3Gy vs 4.0 ± 1.4Gy	Secondary cancer risk – estimates for lung cancer only

						Left ventricle - 6.5 ± 1.6Gy vs 1.9±1.5Gy vs 1.9±1.6Gy No difference for liver/kidney/stomach/spleen/bowels Estimated risk per 10,000 patient years (VMAT vs PBT): Secondary cancer (EAR) - 19.2 ± 5.7 vs 6.1 ± 2.7 Cardiac failure (RR) - 1.5 ± 0.1 (VMAT) and 1.1 ± 0.1 (PBT) Coronary artery disease (RR) - 1.6 ± 0.4 (VMAT) and 1.2 ± 0.3 (PBT)	
Warren et al., 2017[51]	Planning study	n = 21 Mid-tumours only	Definitive 50Gy/25# (PTV) 62.5Gy/25# (GTV+5mm)	PBS	VMAT 3DCRT	PBT superior: Bone – mean, V10; Thoracic vertebrae (TV) – mean dose. No difference: Other bone/TV parameters.	More significant bone sparing with PBT for patients with larger PTV
Warren et al., 2016[52]	Planning Study	n = 21 Mid-tumours only	Definitive 50Gy/25# (PTV) 62.5Gy/25# (GTV+5mm)	PBS	VMAT	PBT superior: Lung – Mean, V20; Heart – Mean, V5, V30. No difference: Cord (Dmax) CTV coverage (for nominal plans)	For dose escalation: VMAT – constraints met for 16/21 cases PBT – constraints met for 20/21 cases PBT - CTV coverage less robust to setup errors

Abbreviations: MDACC = MD Anderson Cancer Centre, Houston, USA ; PMRC/UoT = Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan; NCCJ = National Cancer Center Japan, Chiba, Japan; LLUMC = Linda Loma University Medical Centre, Linda Loma, USA; Mayo = Mayo Clinic, Phoenix, USA; SCCA/UoW = SCCA Proton Therapy Centre/University of Washington, Seattle, USA; Gy = Gray; NA = neoadjuvant; PBT = proton beam

therapy; PS = passive scattering; PBS = pencil beam scanning(also referred to as spot-scanning and IMPT); IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc therapy; 3DCRT = 3D conformal radiotherapy; GTV = gross tumour volume; CTV = clinical target volume; PTV = planning target volume; AC = adenocarcinoma; SCC = squamous cell carcinoma; RCA = right coronary artery; LCX = left circumflex; RA = right atrium; LA = left atrium; LV = left ventricle; RV = right ventricle; LMC = left main coronary artery; LAD = left anterior descending; LPO = left posterior oblique; RPO = right posterior oblique; AP = anterior-posterior; PA = posterior-anterior; CI = conformity index; UI = uniformity index; HI = homogeneity index; TV = thoracic vertebrae; EAR = Excess absolute risk; RR = relative risk; 2F = 2-field; 3F = 3-field.

Table 3: Clinical Studies

Reference	Summary of study design	No. of Patients (n) and tumour description	Radiotherapy description	PBT type	Comparison	Results	Additional notes
Lin et al., 2020[53]	Prospective (Phase II RCT), Single centre (MDACC)	n=107 (IMRT, n=61; PBT, n=46) Mixed histology/ location, mostly distal AC tumours	Definitive/NA (47.4% had surgery) Mostly 50.4Gy/28# with chemotherapy	PS (80%) /PBS	IMRT	Total Toxicity Burden (TTB)* -posterior mean TTB was 2.3 times higher for IMRT vs PBT. Post-operative complications (POC) score was 7.6 times higher for IMRT vs PBT. Survival - Comparable 3yr PFS rate (50.8% v 51.2%) and 3-year OS rates (44.5% v 44.5%).	145 patients randomised Co-primary endpoints were TTB and PFS. *TTB is a composite score of 11 distinct adverse events including post-operative complications.
Shiraishi et al., 2018[54]	Retrospective , Single centre (MDACC)	n=480 (n= 272 in propensity matched analysis) Mostly distal AC	NA 50.4Gy/28# With chemotherapy	PS/PBS	IMRT	PBT - 71% risk reduction of G4 lymphopenia. IMRT/older age/larger PTV results in higher rate of G4 lymphopenia. OS/PFS/DMFS better in absence of G4 lymphopenia.	Multivariate/univariate logistic regression models used to identify factors associated

							with G4 lymphopenia
Lin et al., 2017[55]	Retrospective, Single centre (MDACC)	n=580 Mostly distal AC tumours	NA 50.4Gy/28# with chemotherapy	PS/ PBS	3DCRT IMRT	*PBT vs 3DCRT/IMRT* PBT superior (post-op): Pulmonary complications (OR 0.447); cardiac complications (OR 0.518); wound complications (OR 0.266); reduced length of hospital stay. No difference: 90 day post-op mortality rates - 4.2%, 4.3%, and 0.9%, respectively, for 3D, IMRT and PBT (p=0.264) *PBT vs IMRT alone*: Trend to reduction in pulmonary complications (p=0.077); No difference in cardiac complications (p=0.695).	
Wang et al., 2020 [41]	Retrospective analysis of G3+ Cardiac events, Single centre (MDACC)	n=479 (PBT=159; IMRT, n=320)	Definitive/NA 41.4Gy/23# - 50.4Gy/28# With chemo	PS/PBS	IMRT	G3+ Cardiac events in 18% of total cohort. Median 7m post-RT, 81% within 2 years. Fewer G3+ cardiac events in PBT group vs IMRT, at 2yrs - 18% vs 11%, p=0.053. Mean heart dose correlated with rate of G3+ Cardiac Events (HR 1.034, 95% CI 1.006-1.062, p=0.015)	Dosimetric outcomes reported in Table 2

Chen et al. (2019) [56]	Prospective Phase I/II trial of dose escalation, Single centre (MDACC)	n=46 (PBT, n=7; IMRT, n=39) Mixed histology/location	Definitive/NA 50.4Gy/28# + SIB to GTV (3mm) to 63Gy/28#	n/a	Dose escalation study, single arm	PBT vs IMRT: No difference in local control No difference in overall survival Whole trial cohort vs contemporaneous cohort: SIB had superior local control (hazard ratio, 0.49; 95% CI, 0.26-0.92; P = .03) and overall survival (hazard ratio, 0.66; 95% CI, 0.47-0.94; P = .02)	Trial primarily assessing safety and feasibility of SIB. No randomisation or endpoints related to PBT.
Zeng et al., 2016[48]	Retrospective, Single centre (UoW/SCCA)	n = 13 Mid and distal tumours, SCC/AC	NA 50.4Gy/28# with chemotherapy	PS/ PBS	PBT beam arrangements PS vs PBS	pCR rate - 25% G3 oesophagitis – 7.7% G3 neutropenia – 7.7% G3 nausea – 7.7% Post op pulmonary toxicity – 33.3% Post op cardiac toxicity – 16.7% No difference in toxicities or outcomes with PS vs PBS	Dosimetric outcomes reported in Table 2
DeCesaris et al., 2020 [57]	Retrospective, Single centre (UMMC)	n=54 (PBT, n=18; Photons, n=36) Distal/GOJ AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT	pCR rate – No difference, 7% *vs.* 22% (PBT vs IMRT), (p=0.63) 18m OS – No difference, 83% (95% CI, 71% to 95%) vs. 59% (95% CI, 50% to 68%) (PBT vs IMRT) (p=0.31) Major peri-operative events – no difference 19% vs 22% (PBT vs IMRT) 5 perioperative deaths with IMRT, 0 in PBT arm	Unmatched tumour characteristics with PBT patients having higher tumour and nodal stages

Macomber et al., 2018[47]	Retrospective, Single centre (LLUMC)	n =55 (PBT, n= 18; IMRT, n=21; 3DCRT, n=16) Mostly distal AC	NA 50.4Gy/28# with chemotherapy	PBS	IMRT 3DCRT	Median OS - 73 months, 1yr OS - 92% 2yr OS - 77%. pCR rate -20% No correlation between heart dose/radiation modality and clinical outcomes	Dosimetric outcomes reported in Table 2
Prayongrat et al., 2017[42]	Retrospective, Single centre (MDACC)	n=19	Definitive/NA 50.4Gy/28# with chemotherapy	PBS	-	G3-4 oesophagitis – 15.8% G3-4 haematological tox – 10.5% G1-2 cardiac – 15.8% G1 Pleural effusion – 15.8% No cases of pneumonitis 1yr OS - 100% 2yr OS - 87.5% 2yr PFS - 50.6%	Dosimetric outcomes reported in Table 2
Bhangoo et al. (2020)[58]	Retrospective, Single Centre (Mayo)	n=62 (PBT=32, IMRT=32) Mixed histology/location, mostly distal AC	Definitive/NA (53.2% had surgery) 45Gy/25# with boost to 50Gy (median)	PBS	IMRT	pCR rates – 33% vs 39% (p=0.14) G3 Tox – no difference (p=0.71) *1yr outcomes* Local control – 92% vs 84% (p=0.87) 1 yr LRCR = 92% vs 80% (p=0.76) PFS - 71% vs 45% (p=0.15) OS - 74% vs 71% (p=0.61)	Imbalanced patient characteristics in both arms
Routman et al., 2019[59]	Retrospective, Single centre (Mayo)	n = 144 (PBT, n=65; photon, n=79) Mostly AC, lower With chemotherapy	Definitive/NA 41.4-50.4Gy/23-28#	PBS	3DCRT IMRT	Whole cohort uni/multivariate models: CTV per 100 cm3, stage III/ IV and photon RT associated with higher rates of G4 Lymphopenia Propensity matched cohort (n=100):	PBT used RPO/LPO beam arrangement

						G4 lymphopenia rate – PBT 24% vs Photon 60%. [OR 4.75 (2.01-11.24), P < .001]	
Lin et al., 2012[60]	Retrospective, Single centre (MDACC)	N = 62 Mix histology Mostly AC and lower third	Definitive/ NA 50.4Gy/28# With chemotherapy	PS	-	Selected Toxicity: G3-5 Lung -1.6% G3-5 Oesophagitis-9.7% 3yr outcomes(estimated) OS – 51.7% RFS - 40.5% DMFS – 66.7% LRCR – 56.5%	Likely overlap of patients in Lin et al. (2017)[55] paper. 46.8% underwent surgical resection
Fang et al., 2018[61]	Retrospective, Single centre (MDACC)	n=448 (n=220 in propensity matched analysis) Mostly AC, lower third tumours	Definitive 45-50.4Gy/25-28# With chemotherapy	-	IMRT	IMRT associated with more G4 lymphopenia (OR 2.13 (1.19-3.81), P < .01) Reduction lymphocyte count/higher stage/greater PTV associated with worse OS. PBT benefitted lower third tumours more in reducing rate of G4 lymphopenia Radiation modality not associated with OS	Patients who developed distant metastases within 1 month of RT (21%) excluded from analysis
Xi et al., 2017[37]	Retrospective, Single centre (MDACC)	N = 343 (PBT, n=132, IMRT n=211)	Definitive 50.4/28#	PS/PBS	IMRT	No difference in toxicities between both groups	Unmatched patient

		Mostly AC and lower tumours	With chemotherapy			5yr outcomes vs IMRT: OS – 41.6% vs 31.6% (p=.011) PFS – 34.9% vs 20.4% (p=0.01) DMFS – 64.9% vs 49.6% (p=0.31) LRRFS – 59.9% vs 49.9% (p=0.75) Patients with stage III disease in subgroup analysis: 5yr OS (34.6% vs 25.0%, p = 0.038) 5yr PFS (33.5% vs 13.2%, p=0.005) No difference for Stage I/II patients	baseline characteristics Additional analysis with some matched characteristics show PBT still superior for OS, PFS, LRFFS and DMFS Dosimetric outcomes reported in Table 2
Takada et al., 2016[62]	Retrospective, Multi-centre (Japanese centres)	N = 47 Mostly SCC, mix location	Definitive Two phase RT First phase -3DCRT 36Gy/20# 2nd phase PBT, 33-39.6Gy/15-18# with chemotherapy	n/a	-	Selected results: Early toxicity– 10.6% oesophagitis G3 late toxicity – 1 oesophageal fistula, 2 oesophageal stenosis, 1 pneumonitis 3yr OS, PFS, LC – 59.2%, 56.3%, 67.7% respectively	
Ishikawa et al., 2015[63]	Retrospective, Single centre (PMRC/UoT)	N = 40 Mostly upper and middle third tumours Histology n/a	Definitive 50-60Gy/30# With chemotherapy	PS	-	G3 oesophagus acute tox -22% G3 oesophagus late tox -5% No grade 3-5 acute or late cardiac/pulmonary toxicity 2yr LRC - 66.4%, CSS – 77.4% 3yr OS – 70.4%	Patients endoscopically assessed at 50Gy with 40% given 4-10Gy boost if residual tumour

Mizumoto et al., 2010[64]	Retrospective ,mostly single centre (PMRC/UoT)	n = 51 Mostly SCC	Definitive Photon RT with PBT boost (n=33) Median dose - 80Gy over 59 days PBT alone (n=18) Median dose - 79Gy over 57 days (33-64 days) No chemotherapy	PS	-	G3 oesophagitis 12% Post RT ulceration - 49% 1yr: OS-62.2%,PFS – 45.5%, LRCR- 64.5% 3yr: OS – 34.3%, PFS – 24.6%, LRCR – 42.8% 5yr: OS - 21.1%, PFS – 24.6%, LRCR – 38.0%	Patients treated from 1985-2005
Mizumoto et al., 2011[65]	Retrospective , Single centre (PMRC/UoT)	n = 19 Mostly SCC	Definitive 78gy (median) No chemotherapy	PS	-	One G3 oesophagitis 1 yr OS 79.0% 5 yr OS 42.8%	Patients from 1990 – 2007 Potential overlap in patient cohort with Mizumoto et al. 2010[64]
Ono, Wada, Ishikawa, Tamamura, & Tokumaru, 2019[66]	Retrospective , Multi centre (4 Japanese centres)	n = 202 Mostly thoracic SCC	Definitive 87.2 Gy (Median dose, Mix Photon and PBT RT) With/without chemotherapy (59.7% received chemotherapy)	PS/PBS	-	G2 oesophageal fistulas – 4% (n=8) G3 oesophageal ulcer – 4% G3 Pneumonitis – 0.5% 3 yr OS - 66.7%, LC- 70.2% 5 yr OS - 56.3%, LC – 64.4%	
Ono et al., 2020 [67]	Retrospective , Multi centre	n=38, Thoracic SCC, All aged ≥75 years	Definitive	PS/PBT	-	G3 ulcers – 5.3% No lung/heart G3 toxicities	59.3% had Stage I/II disease

	(4 Japanese centres)		82.7Gy (Median dose, Mix Photon and PBT RT) With/without chemotherapy (42.6% received chemotherapy)			Median survival – 64m 2 yr OS: 74.9% 3yr OS: 66.2% 5yr OS: 56.2%	Ono et al. 2015 [68] excluded – likely overlap in patient cohort.
Sato et. al., 2020 [69]	Retrospective, Single centre (NCCE)	n=44 SCC only All T1 with mostly N0/N1 disease	Definitive 60Gy with chemotherapy	n/a	-	G3 oesophagitis – 2.3% No G4 toxicity CR rates – 98% 3yr OS – 95.2% Local recurrence – 11%, all underwent salvage treatment	All patients underwent close endoscopic follow-up
Makishima et al., 2015[46]	Retrospective, Single centre (PMRC/UoT)	n= 44 (PBT, n=25 photon, n=19) SCC only	Definitive Median dose 60Gy (40Gy to CTV1, 6-Gy to CTV2) with chemotherapy	PS	3DCRT	PBT toxicity: Mostly G1 lung and heart except one G2 cardiac 3DCRT toxicity: Mostly G1, 16 episodes G2/3 lung and cardiac, one G5 lung.	Dosimetric outcomes reported in Table 2 Unmatched patient characteristics Higher rate of adverse events in PBT compared to NTCP models

Abbreviations: MDACC = MD Anderson Cancer Centre, Houston, USA ; PMRC/UoT = Proton Medical Research Centre, University of Tsukuba, Tsukuba, Japan; NCCE = National Cancer Centre East, Kashiwa, Japan; LLUMC = Linda Loma University Medical Centre, Linda Loma, USA; Mayo = Mayo Clinic, Rochester, USA; SCCA/UoW = SCCA Proton Therapy Centre/ University of Washington, Seattle, USA; UMMC = University of Maryland Medical Centre, Baltimore, USA; RCT =

randomised controlled trial; NA = neoadjuvant; Gy = Gray; PBT = proton beam therapy; PS = passive scattering; PBS = pencil beam scanning [also known as spot-scanning, intensity modulated proton therapy(IMPT)]; IMRT = intensity modulated radiotherapy; VMAT = volumetric arc therapy; 3DCRT = 3D conformal radiotherapy; SIB = Simultaneous Integrated Boost; GTV = gross tumour volume; CTV = clinical target volume; PTV = planning target volume; AC = adenocarcinoma; SCC = squamous cell carcinoma; RPO = right posterior oblique; LPO = left posterior oblique; TTB = total toxicity burden; POC = post-operative complication; G1-5 = Grade 1-5; mOS = median overall survival; OS = overall survival; PFS = progression free survival; DMFS = distant metastases free survival; RFS = relapse free survival; LCRC = locoregional control rate; LRRFS = locoregional relapse free rate; LRC = locoregional control; CSS = cancer specific survival; LC = local control; pCR = pathological complete response; NTCP = normal tissue complication probability; EAR = excess absolute risk.

Discussion

Dosimetric Studies

All studies are retrospective or planning studies with most using data from single institutions. There is a substantial variation in radiotherapy intent, dose, chemotherapy protocol, type of tumour, tumour location and PBT technique (PS/PBS) used in these studies. The studies generally reported multiple dosimetric parameters for lung, heart and spinal cord. They consistently show an overall reduction in dose to the heart and lung although not in all reported parameters. Notably, target volume(GTV/CTV/PTV) coverage are not reported in all studies. The studies which include target volume statistics report comparable coverage to photon techniques.[37, 39, 42, 52] Clinical outcomes were reported in some of these studies and are detailed in the following section.

Heart and Lung doses

For cardiac doses, there is a general reduction in most parameters, with the exception of a few studies which showed no significant difference in mean heart dose [37, 40] and another which reported no difference in V50 heart [47]. For patients with lower third tumours in which CTV/PTV is often incident with the heart, there is still significant reduction in dose for most reported parameters. Shiraishi et al. reported that dose to all cardiac substructures other than to the left circumflex (LCX) and right coronary artery (RCA) are significantly reduced compared to IMRT. [38] Wang et al. (2020) reported that dose parameters correlated with rates of Grade 3 and above (G3+) cardiac events in their retrospective cohort. [41]

For the lung, there is a consistent reduction in most parameters. Predictably, in the absence of a 'low-dose bath' associated with IMRT, lower dose parameters such as mean dose, V5 and V10 showed very significant dose reduction in comparison with IMRT/VMAT with some studies reporting an approximately 50% reduction. [37, 46, 54] For higher dose parameters such as lung V40, Wang et al. (2015) reports that PBT is inferior to IMRT although these volumes are small. [40] In another study, Celik et al. [50] estimated a lower dose to lung resulted in a reduction of excess absolute risk

(EAR) of secondary lung cancers per 10,000 patient years of nearly 70% with PBT(19.2 ± 5.7) compared to VMAT (6.1 ± 2.7).

Other OARs

For the spinal cord, there appears to be a comparable or lower dose compared to photon techniques. [39, 40, 43, 45, 52] Warren et al. report that mean dose to thoracic vertebrae and bone is significant reduced with proton beam therapy. This is postulated to reduce the risk of haematological toxicity including lymphopenia. [51] Dose to liver and stomach is reported in several studies, with all meeting standard dose constraints. For reported parameters, the dose to liver is consistently reduced, the clinical impact of which is uncertain.

Beam arrangements

Three studies compared the dosimetric outcomes of different combinations of PBT beam arrangements for oesophageal tumours.[39, 48, 49]. Zeng et al. showed multiple combinations of beams could comfortably achieve dose and target constraints with the authors concluding that even a single PA (posterior-anterior) beam is a feasible option. This paper demonstrated that different beam arrangements preferentially spared different OARs. For example, AP (anterior-posterior)/PA beams resulted in a higher heart dose, but lower lung dose compared to a PA/LPO (left posterior oblique) arrangement. [48] A recent paper by Feng et al. showed that a novel superior-inferior posterior oblique beam arrangement was a feasible option and compared to right-left posterior oblique beams, may result in lower lung doses and greater robustness to respiratory motion when interplay effects are considered. [49]

Multiple different beam arrangements appear clinically acceptable with different arrangements preferentially sparing different OARs with adequate target volume coverage. This suggests PBT may allow, to a greater degree than photons, a personalised approach to the radiotherapy planning that may be tailored to the underlying comorbidities of individual patients.

Clinical studies

There is only one prospective study of PBT in oesophageal cancer. We identified a further prospective trial which included PBT data, but this primarily assessed dose escalation in oesophageal cancer. All other published clinical outcome data for PBT in oesophageal cancer is retrospective with most patients treated in a single US centre (MDACC). Despite sizable patient numbers in some studies, it is likely that several articles report findings based on overlapping patient cohorts. There is significant variation in type and location of tumours treated, tumour operability at presentation, treatment intent, dose, fractionation, PBT technology used, follow-up schedule and reported outcomes.

Prospective data

This study by Lin et. al [53] is a Phase IIB single centre (MDACC) RCT that compared patients who received PBT in the NA and definitive setting to those receiving IMRT. While most patients received a dose of 50.4Gy/28# (91.6% of patients), there is significant variation in type of chemotherapy. Chemotherapy regiments used included: fluorouracil (5-FU) and capecitabine (X) plus taxane (T)(55.1% of patients), Carboplatin (CP) plus T(21.5% of patients) and 5-FU plus Oxaliplatin (OX)(18.7% of patients). The primary endpoint of this trial was total toxicity burden (TTB) and PFS. TTB is a novel composite score of 11 adverse events that relies on a multivariate Bayesian model that accounts for the incidence and severity of each type of toxicity including post-operative complications (POCs).[70] The POCs were assessed at 30-days post op and included 6 potentially recurrent toxicities at 12 months. The study reported that mean TTB was 2.3 times higher for IMRT and mean POC score was 7.6 times higher for IMRT implying a significant reduction of toxicity burden for patients receiving PBT. Three-year PFS and OS for both arms showed no significant difference. This trial was approved for early closure and analysis by the data safety monitoring board in early 2019, before the activation of the multi-centre Phase 3 NRG-GI006 study of proton versus photons in oesophageal cancer (NCT03801876).

While TTB is a rational metric that encompasses the complex multi-organ effects of tri-modality treatment, it is yet to be widely validated outside the trial. The trial also included patients that did not have surgery and suffered significant dropout rates post-randomisation to the PBT arm mainly due to insurance denial. Of the 145 patients randomised, only 21 patients proceeded to surgery following PBT. In addition, the radiotherapy dose and chemotherapy used in the trial were heterogenous although balanced between both arms. Despite these limitations, these results are undoubtedly promising. It confirms the safety of PBT treatment and provides the first prospective data showing that dosimetric advantage translates to significantly improved toxicity outcomes. The findings of the currently recruiting phase 3 NRG-GI006 study are eagerly anticipated.

Of note, there is a further prospective study by Chen et al. included in this review. However, this was a Phase I/II study that primarily assessing safety and feasibility of SIB with no randomisation or pre-specified endpoints related to PBT. In this study, there was no difference in OS or PFS for patients who received either PBT or IMRT. [56]

Neoadjuvant (NA)

There are several retrospective studies which reported on the use of NA PBT. In this setting a dose of 50.4Gy/28# is predominantly used; significantly higher than dose used in the CROSS trial of 41.4Gy/23#. Lin et al. (2017) gives a comprehensive report of post-operative complications, with PBT resulting in lower pulmonary, cardiac, wound complications and reduced length of hospital stay compared to photon techniques (3DCRT/IMRT).[55] However, compared to IMRT alone, the current standard of care for many centres, there is only a trend to lower pulmonary complications and no difference in cardiac complications. Another study by Shiraishi et al.,[54] showed there was a lower rate of G4 lymphopenia in the PBT group which in turn, correlates with improved survival outcomes and local control rates. In a separate study that included 46.8% of patients who underwent surgery, Lin et al. (2012)[60] reported favourable 3yr survival outcomes and local control rates which are at least comparable to reported randomised controlled trial data.[5]

While these data are promising, it is unclear if these potential benefits translate when a lower dose fractionation is used as is common in European practice. Additionally, as surgery is often not mandatory in many American centres, as seen in Lin et al.'s prospective study, these data are prone to inadvertent reporting bias, particularly when considering post-operative complications. Further prospective trials with robust radiotherapy and surgical protocols are required to accurately elucidate the benefits of PBT in this setting.

Definitive

Most studies reported the use of PBT in the definitive setting for oesophageal cancer. There is a substantial variation in radiation dose/protocol and use of chemotherapy. Most studies used a dose of 50-60Gy, comparable to current guidelines[71]. Several studies from Japan report outcomes using a dose-escalated schedule with PBT in combination with photon RT. Ono et al. (2019) [66] delivered a median dose of 87.2Gy; significantly higher than doses commonly used in European centres.[72] While most toxicities appear acceptable, 8 patients developed oesophageal fistulas (G2+) post-RT.

Some studies looked predominantly at patients with SCC of the oesophagus. Here, 3yr overall survival rates range from 34.3% to 70.4% which is comparable or superior to most published data [73] with acceptable toxicities. The largest cohort (Ono et al (2019), n =202)[66] reported impressive 3yr and 5yr OS of 66.7% and 56.3% respectively. However, there was significant variation in treatment delivered e.g. 72.7% received elective nodal irradiation (58.9% with photons) and only 59.7% received concurrent chemotherapy. The study also included 55.4% of patients with operable disease, including 35.6% with Stage 1 disease, making survival outcomes difficult to interpret. The same group also published data on smaller cohort of patients aged above 75 years with mostly with early stage tumours using a median dose of 82.7Gy. This showed a promising median survival of 64 months for an elderly patient group with acceptable toxicity rates albeit with G3 ulcer rate of around 5%.[67]

Studies that treated predominantly AC of the oesophagus generally did not exceed 50.4Gy in combination with chemotherapy. Here toxicity rates appear comparable or lower than photon techniques except for G4 lymphopenia which is lower in PBT in all reported studies. Survival outcomes appear at least comparable or superior to photon RT. In a single centre retrospective cohort, Xi et al. superior OS and PFS with a 5yr OS of 41.6% (PBT) vs 31.6% (IMRT) (p = 0.011), and 5yr PFS rates of 34.9%(PBT) vs 20.4%(IMRT) (p=0.01)[37]. Fang et al., however, in a propensity matched analysis of PBT vs IMRT, found that OS was not associated with radiation modality.[61]

Cardiac Toxicity

A study by Wang et al.[41] specifically assessed cardiac event rates in a retrospective cohort (treated both definitively and NA) and found PBT resulted in fewer serious cardiac events(G3+) vs IMRT [IMRT vs PBT: 2yr rate 18% vs 11%; 5yr rates 21% vs 13%; p= 0.053] . Moreover, their analysis showed PBT had a greater reduction in patients with underlying cardiovascular disease [IMRT vs PBT: 2yr 30% vs 11%; 5yr rates 32% vs 14%; p= 0.018)]. Their analysis showed that mean heart dose of <15gy was associated with fewer serious cardiac events. The median length time to a serious cardiac event was seven months with 81% of events occurring within two years. A separate study by Lin et al. [55] that reviewed post-operative complications showed no difference in cardiac complication rates with PBT. These studies suggest that PBT may not have an impact on cardiac complications in the immediate post-operative period but may significantly reduce cardiac toxicities in the medium term (from 3 months - 2 years post-RT), especially for high risk patients with underlying cardiac disease.

Grade 4(G4) Lymphopenia

The rate of G4 lymphopenia is an emerging predictive bio-marker, correlating negatively with survival and local control rates post-RT for a number of tumour sites [74, 75]. This clinical endpoint has been reported by several studies included in this analysis. Three studies [54, 59, 61] used in both the NA setting and definitive settings showed PBT reduced the incidence of G4 lymphopenia, with the rate appearing to correlate with an increased size of PTV and a lower tumour location. The reasons for a reduction of G4 lymphopenia with PBT is not completely established but is likely to be

related to a reduced integral and OAR dose compared to photon RT techniques. A planning study by Warren et al. [51] reported a lower dose to bone which may provide a dosimetric rationale for this outcome. A more recent study suggests dose to circulating immune cells may be a contributing factor including during cardiac irradiation. [76] In their entire surgical cohort, Shiraishi et al. [54] showed that absence of G4 lymphopenia was associated with better OS and PFS. However, in their matched analysis, there remained a PFS advantage but only a trend towards improved OS.

Passive scattering (PS) vs Pencil beam scanning (PBS)

Historically, PBT to the oesophagus was delivered using PS technology which is less conformal, particularly to tissues proximal to target volume, compared to newer PBS (spot-scanning/IMPT) technology. [77] Outside the US and Japan, most centres are equipped with only PBS technology. [24] Two studies compared outcomes between the technologies. Shiraishi et al. found that most cardiac substructures received lower doses with PBS compared to PS, [38] while Zeng et al. found no difference in toxicities between the two technologies[48]. Most other studies grouped the results of PBS and PS, making analysis difficult.

Other technical considerations of delivering PBT to oesophagus

Uncertainties in PBT may result in a dose displacement and a distortion of delivered dose resulting in potential underdosing of targets volumes and overdose of OARs. The range uncertainty in protons is due, in part, to uncertainties in calibration of the patient's CT to relative proton stopping powers and the handling of tissue heterogeneities by analytical dose algorithms.[78] This is especially pronounced for regions with large density heterogeneities such as the oesophagus. Factors such as intra-fraction motion [e.g. due to breathing (causing interplay effects), peristalsis] and inter-fraction changes (e.g. weight loss, tumour progression) further compound these uncertainties.[79] Multiple strategies have emerged to mitigate these uncertainties including robust optimisation/analysis[80, 81], rescanning[82], advanced on-treatment imaging/verification(image guided RT)[83], use of more accurate dose algorithms (e.g. Monte-Carlo)[78], and motion management techniques (e.g. breath-hold, gating)[84]. Many studies included in this analysis were carried out without the benefit of

many of these recent technological advances. For example, Lin et al.'s (2020) [53]prospective study, which commenced recruitment in 2012, used daily kV imaging rather than cone beam CTs for treatment verification of PBT patients. The rapid development and adoption of new technologies such as advanced treatment planning systems, on-board volumetric imaging and motion analysis are likely to improve the certainty of delivered dose for future patients.

Another emerging area of interest is the impact of variable proton RBE on control rates and toxicity outcomes.[85] While this is a complex and emerging topic that is outside the scope of this review, it is important to note that all studies included in this review used RBE factor of 1.1 for PBT indicating that this remains a standard approach for most centres. All published clinical outcomes of PBT are at least comparable or superior to photons, with no unexpected toxicity signals, providing reassurance of the safety of PBT to the oesophagus despite these uncertainties.

Conclusion

There is a growing body of evidence supporting the use for PBT in oesophageal cancer in both the NA and definitive setting. However, most evidence is of low quality, being based mainly on retrospective cohorts with only one prospective study. The substantial variation in intent, techniques, dose, fractionation and use of chemotherapy means the role and 'gold-standard' protocol for PBT in oesophageal cancer is yet to be defined.

Based on current evidence, dosimetric advantages over photon techniques are substantial and difficult to refute. In particular, low dose parameters of the lung are significantly reduced with PBT. Clear but less substantial reductions are seen with cardiac (whole heart/substructures), spinal cord and liver doses. Target volume (GTV/CTV/PTV) coverage appears comparable but is not consistently reported in all studies.

For the clinical outcomes there appears to be a significant pattern of reduction in toxicity burden as reported in the published prospective study and other large retrospective cohorts. Importantly, there is a significant decrease in rate of post-operative lung and heart toxicities, wound healing and length of hospital stay. Beyond the immediate post-operative period, emerging data suggests that PBT reduces the incidence of severe cardiac events and reduces the risk of secondary lung cancers. The impact of PBT on survival outcomes are less obvious. Prospective data suggests it is at least equivalent to photon RT techniques and demonstrates the safety of PBT in oesophageal cancer. Some studies showed an improvement in PFS and at least a trend to improved OS in comparison to photon techniques but again, the quality of evidence is low and based on mainly single-centre, retrospective cohorts. There is currently no evidence suggesting that variable proton RBE results in either superior control rates or unexpected toxicities. Importantly, most published studies have a limited follow-up period of several years, meaning long-term effects on survival of OAR sparing may yet be seen. Grade 4 lymphopenia, an emerging biomarker for poor survival in oesophageal cancer, may be a potential influence on improving survival outcomes with PBT.

An area which is not explored in detail in this review is the high cost of PBT treatment and additional resources required to deliver these treatments. This is outside the scope of this review. However, it is essential resource implications are systematically assessed in any future PBT trials by including robust and transparent health economic analyses as suggested by a recent review by Jones et al. [27]. This includes appropriate use of patient reported outcomes measures (PROMs) with longer term follow-up to assess late toxicities. Studies included in this review show that PBT has the potential to reduce late toxicities of treatment including cardiac events and secondary cancer risks suggesting the greater upfront costs of PBT may be justified with longer term savings.

Overall, there remains a glaring paucity of randomised, prospective data advocating the use of PBT with only a single prospective trial published to date despite the significant numbers of patients treated. The groups of patients that will benefit most from PBT are yet to be defined. Future efforts should focus on establishing a robust evidence base for the use of PBT in oesophageal cancer with well-designed, prospective clinical trials such as the NRG-GI006 study. These studies should have quality-assured standardised protocols to ensure real-world reproducibility of results, robust health economic analyses to ascertain accurate cost/benefit ratios from PBT and include patient-focussed endpoints such as toxicity reduction and overall survival. Future work should also include the development of predictive biomarkers to determine patients who will benefit most from PBT, the incorporation of advanced planning techniques (e.g. LET-based planning) and image guidance.

While there is currently insufficient evidence to recommend PBT as a standard of care, it undoubtedly holds substantial promise in the treatment of oesophageal cancer; potentially improving outcomes for a cancer that continues to have a dismal prognosis. For this, PBT clearly warrants urgent further evaluation.

Appendix a

Full Search Terms

Database: Embase <1996 to 2020 December 15> Searched 17/12/20
Search Strategy:
---
1 esophageal carcinoma$.tw. (6983)
2 oesophageal carcinoma$.tw. (975)
3 esophageal neoplasm$.tw. (435)
4 oesophageal neoplasm$.tw. (37)
5 esophageal tum#r$.tw. (1693)
6 oesophageal tum#r$.tw. (34)
7 esophageal squamous cell carcinoma$.tw. (12227)
8 oesophageal squamous cell carcinoma$.tw. (879)
9 (cancer$ adj3 oesophag$).tw. (5975)
10 (cancer$ adj3 esophag$).tw. (32237)
11 (adenocarcinoma$ adj2 esophag$).tw. (8252)
12 (adenocarcinoma$ adj3 oesophag$).tw. (2353)
13 exp esophagus cancer/ (64282)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (77193)
15 proton beam therapy.tw. (1765)
16 proton therapy.tw. (5800)
17 proton beam radiation therapy.tw. (181)
18 proton radiation therapy.tw. (417)
19 proton therapy/ (8914)
20 trimodalit$ therap$.tw. (892)
21 15 or 16 or 17 or 18 or 19 or 20 (11067)
22 14 and 21 (546)
23 limit 22 to (human and english language and yr="2010 - 2021") (466)
(8 Anonymous papers removed – conference round ups)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to December 15, 2020> Searched 17/12/20
Search Strategy:
---

1 esophageal carcinoma$.tw. (6358)
2 oesophageal carcinoma$.tw. (1045)
3 esophageal neoplasm$.tw. (447)
4 oesophageal neoplasm$.tw. (36)
5 esophageal tum#r$.tw. (1522)
6 oesophageal tum#r$.tw. (37)
7 esophageal squamous cell carcinoma$.tw. (9080)
8 oesophageal squamous cell carcinoma$.tw. (780)
9 (cancer$ adj3 oesophag$).tw. (4570)
10 (cancer$ adj3 esophag$).tw. (25346)
11 (adenocarcinoma$ adj2 esophag$).tw. (5149)
12 (adenocarcinoma$ adj3 oesophag$).tw. (1548)
13 proton beam therapy.tw. (1160)
14 proton therapy.tw. (3185)
15 proton beam radiation therapy.tw. (118)
16 proton radiation therapy.tw. (248)
17 trimodalit$ therap$.tw. (443)
18 exp Esophageal Neoplasms/ (51260)
19 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 18 (64347)
20 exp Proton Therapy/ (3845)
21 13 or 14 or 15 or 16 or 17 or 20 (6104)
22 19 and 21 (243)
23 limit 22 to (english language and humans and yr="2010 - 2021") (134) –all already identified via EMBASE

Web of Science Searched 17/12/20

esophag* (Topic) and **carcinoma* OR cancer* OR neoplasm* OR tumor*** (Topic) and **"proton beam" OR "proton therapy"** (Topic) and **2020 - 2010** (Publication Years)

136 references – 2 unique added to Endnote

COCHRANE LIBRARY

Checked – no additional refs 17/12/2020

Table 3- Full search terms for systematic review

Appendix b

Table 4 PRISMA Checklist for Systematic Reviews

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1, Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a

Section/topic	#	Checklist item	Reported on page #
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a

Section/topic	#	Checklist item	Reported on page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	25-34
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	n/a
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33-34
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

References

1. Bray, F., J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, and A. Jemal, *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: A Cancer Journal for Clinicians, 2018. **68**(6): p. 394-424.
2. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer.
3. *https://www.cancerresearchuk.org/funding-for-researchers/our-research-strategy*.
4. *https://www.cancerresearchuk.org/sites/default/files/research-strategy-progress-report-2017.pdf*.
5. Shapiro, J., J.J.B. van Lanschot, M.C.C.M. Hulshof, P. van Hagen, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, et al., *Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial.* The Lancet Oncology, 2015. **16**(9): p. 1090-1098.
6. Low, D.E., M.K. Kuppusamy, D. Alderson, I. Cecconello, A.C. Chang, G. Darling, et al., *Benchmarking Complications Associated with Esophagectomy.* Annals of Surgery, 2019. **269**(2): p. 291-298.
7. *National Oesophago-Gastric Audit (NOGCA) Annual Report 2018. Retrieved from https://www.nogca.org.uk/reports/2018-annual-report/*.
8. Bowden, C. and S. Gwynne, *Neoadjuvant chemoradiotherapy in resectable oesophageal cancer patients: UK practice.* European Journal of Surgical Oncology, 2016. **42**(11): p. S225.
9. Al-Batran, S.-E., N. Homann, C. Pauligk, T.O. Goetze, J. Meiler, S. Kasper, et al., *Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial.* The Lancet, 2019. **393**(10184): p. 1948-1957.
10. Crosby, T., C.N. Hurt, S. Falk, S. Gollins, J. Staffurth, R. Ray, et al., *Long-term results and recurrence patterns from SCOPE-1: a phase II/III randomised trial of definitive chemoradiotherapy +/- cetuximab in oesophageal cancer.* British journal of cancer, 2017. **116**(6): p. 709-716.
11. Minsky, B.D., T.F. Pajak, R.J. Ginsberg, T.M. Pisansky, J. Martenson, R. Komaki, et al., *INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy.* J Clin Oncol, 2002. **20**(5): p. 1167-74.
12. Voeten, D.M., C.M. den Bakker, D.J. Heineman, J.C.F. Ket, F. Daams, and D.L. van der Peet, *Definitive Chemoradiotherapy Versus Trimodality Therapy for Resectable Oesophageal Carcinoma: Meta-analyses and Systematic Review of Literature.* World J Surg, 2019. **43**(5): p. 1271-1285.
13. *https://www.nice.org.uk/guidance/ng83*.
14. Best, L.M.J., M. Mughal, and K.S. Gurusamy, *Non-surgical versus surgical treatment for oesophageal cancer.* Cochrane Database of Systematic Reviews, 2016(3).
15. Gwynne, S., E. Higgins, A. Poon King, G. Radhakrishna, L. Wills, S. Mukherjee, et al., *Driving developments in UK oesophageal radiotherapy through the SCOPE trials.* Radiation Oncology, 2019. **14**(1): p. 26.
16. Xu, D., G. Li, H. Li, and F. Jia, *Comparison of IMRT versus 3D-CRT in the treatment of esophagus cancer: A systematic review and meta-analysis.* Medicine (Baltimore), 2017. **96**(31): p. e7685.
17. Lin, S.H., L. Wang, B. Myles, P.F. Thall, W.L. Hofstetter, S.G. Swisher, et al., *Propensity Score-based Comparison of Long-term Outcomes With 3-Dimensional Conformal Radiotherapy vs Intensity-Modulated Radiotherapy for Esophageal Cancer.* International Journal of Radiation Oncology*Biology*Physics, 2012. **84**(5): p. 1078-1085.
18. *https://clinicaltrials.gov/ct2/show/NCT02741856*.

19. Welsh, J., M. Palmer, J. Ajani, Z. Liao, S. Swisher, W. Hofstetter, et al., *Esophageal Cancer Dose Escalation Using a Simultaneous Integrated Boost Technique.* International journal of radiation oncology, biology, physics, 2010. **82**: p. 468-74.
20. Hulshof, M.C.C.M., D. Geijsen, T. Rozema, V. Oppedijk, J. Buijsen, K.J. Neelis, et al., *A randomized controlled phase III multicenter study on dose escalation in definitive chemoradiation for patients with locally advanced esophageal cancer: ARTDECO study.* Journal of Clinical Oncology, 2020. **38**(4_suppl): p. 281-281.
21. Crehange, G., A. Bertaut, D. Peiffert, E.L. Prise, P.-L. Etienne, E. Rio, et al., *Exclusive chemoradiotherapy with or without dose escalation in locally advanced esophageal carcinoma: The CONCORDE study (PRODIGE 26).* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 4037-4037.
22. Newhauser, W.D. and R. Zhang, *The physics of proton therapy.* Physics in Medicine and Biology, 2015. **60**(8): p. R155-R209.
23. Paganetti, H., *Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer.* Physics in Medicine and Biology, 2014. **59**(22): p. R419-R472.
24. PTCOG, *https://www.ptcog.ch/index.php/facilities-in-operation (Accessed 2nd April 2020).*
25. Indelicato, D.J., T. Merchant, N. Laperriere, Y. Lassen, S. Vennarini, S. Wolden, et al., *Consensus Report From the Stockholm Pediatric Proton Therapy Conference.* International Journal of Radiation Oncology • Biology • Physics, 2016. **96**(2): p. 387-392.
26. Fossati, P., A. Vavassori, L. Deantonio, E. Ferrara, M. Krengli, and R. Orecchia, *Review of photon and proton radiotherapy for skull base tumours.* Reports of practical oncology and radiotherapy : journal of Greatpoland Cancer Center in Poznan and Polish Society of Radiation Oncology, 2016. **21**(4): p. 336-355.
27. Jones, D.A., J. Smith, X.W. Mei, M.A. Hawkins, T. Maughan, F. van den Heuvel, et al., *A systematic review of health economic evaluations of proton beam therapy for adult cancer: Appraising methodology and quality.* Clinical and Translational Radiation Oncology, 2020. **20**: p. 19-26.
28. Thomas, G., E. Eisenhauer, R.G. Bristow, C. Grau, C. Hurkmans, P. Ost, et al., *The European Organisation for Research and Treatment of Cancer, State of Science in radiation oncology and priorities for clinical trials meeting report.* Eur J Cancer, 2020. **131**: p. 76-88.
29. Price, J., E. Hall, C. West, and D. Thomson, *TORPEdO - A Phase III Trial of Intensity-modulated Proton Beam Therapy Versus Intensity-modulated Radiotherapy for Multi-toxicity Reduction in Oropharyngeal Cancer.* Clinical Oncology, 2020. **32**(2): p. 84-88.
30. Burnet, N., R. Mackay, E. Smith, A. Chadwick, G. Whitfield, D. Thomson, et al., *Proton beam therapy – perspectives on the National Health Service England clinical service and research programme.* The British Journal of Radiology, 2019. **93**: p. 20190873.
31. Crellin, A., *The Road Map for National Health Service Proton Beam Therapy.* Clinical Oncology, 2018. **30**(5): p. 277-279.
32. Speirs, C.K., T.A. DeWees, S. Rehman, A. Molotievschi, M.A. Velez, D. Mullen, et al., *Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer.* J Thorac Oncol, 2017. **12**(2): p. 293-301.
33. Yorke, E.D., A. Jackson, K.E. Rosenzweig, S.A. Merrick, D. Gabrys, E.S. Venkatraman, et al., *Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy.* International Journal of Radiation Oncology*Biology*Physics, 2002. **54**(2): p. 329-339.
34. Darby, S.C., M. Ewertz, P. McGale, A.M. Bennet, U. Blom-Goldman, D. Bronnum, et al., *Risk of ischemic heart disease in women after radiotherapy for breast cancer.* N Engl J Med, 2013. **368**(11): p. 987-98.

35. Wang, J., C. Wei, S.L. Tucker, B. Myles, M. Palmer, W.L. Hofstetter, et al., *Predictors of postoperative complications after trimodality therapy for esophageal cancer.* Int J Radiat Oncol Biol Phys, 2013. **86**(5): p. 885-91.
36. Takeuchi, Y., Y. Murakami, T. Kameoka, M. Ochi, N. Imano, I. Takahashi, et al., *Analysis of cardiac toxicity after definitive chemoradiotherapy for esophageal cancer using a biological dose–volume histogram.* Journal of Radiation Research, 2020. **61**(2): p. 298-306.
37. Xi, M., C. Xu, Z. Liao, J.Y. Chang, D.R. Gomez, M. Jeter, et al., *Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis.* Int J Radiat Oncol Biol Phys, 2017. **99**(3): p. 667-676.
38. Shiraishi, Y., C. Xu, J. Yang, R. Komaki, and S.H. Lin, *Dosimetric comparison to the heart and cardiac substructure in a large cohort of esophageal cancer patients treated with proton beam therapy or Intensity-modulated radiation therapy.* Radiother Oncol, 2017. **125**(1): p. 48-54.
39. Welsh, J., D. Gomez, M.B. Palmer, B.A. Riley, A.V. Mayankkumar, R. Komaki, et al., *Intensity-modulated proton therapy further reduces normal tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study.* Int J Radiat Oncol Biol Phys, 2011. **81**(5): p. 1336-42.
40. Wang, J., M. Palmer, S. Bilton, K. Vu, S. Greer, R. Frame, et al., *Comparing Proton Beam to Intensity Modulated Radiation Therapy Planning in Esophageal Cancer.* International Journal of Particle Therapy, 2015. **1**: p. 866-877.
41. Wang, X., N.L. Palaskas, S.W. Yusuf, J.I. Abe, J. Lopez-Mattei, J. Banchs, et al., *Incidence and Onset of Severe Cardiac Events After Radiotherapy for Esophageal Cancer.* J Thorac Oncol, 2020. **15**(10): p. 1682-1690.
42. Prayongrat, A., C. Xu, H. Li, and S.H. Lin, *Clinical outcomes of intensity modulated proton therapy and concurrent chemotherapy in esophageal carcinoma: a single institutional experience.* Adv Radiat Oncol, 2017. **2**(3): p. 301-307.
43. Hirano, Y., M. Onozawa, H. Hojo, A. Motegi, S. Zenda, K. Hotta, et al., *Dosimetric comparison between proton beam therapy and photon radiation therapy for locally advanced esophageal squamous cell carcinoma.* Radiat Oncol, 2018. **13**(1): p. 23.
44. Ling, T.C., J.M. Slater, P. Nookala, R. Mifflin, R. Grove, A.M. Ly, et al., *Analysis of Intensity-Modulated Radiation Therapy (IMRT), Proton and 3D Conformal Radiotherapy (3D-CRT) for Reducing Perioperative Cardiopulmonary Complications in Esophageal Cancer Patients.* Cancers, 2014. **6**(4): p. 2356-2368.
45. Liu, C., R.S. Bhangoo, T.T. Sio, N.Y. Yu, J. Shan, J.S. Chiang, et al., *Dosimetric comparison of distal esophageal carcinoma plans for patients treated with small-spot intensity-modulated proton versus volumetric-modulated arc therapies.* Journal of applied clinical medical physics, 2019. **20**(7): p. 15-27.
46. Makishima, H., H. Ishikawa, T. Terunuma, T. Hashimoto, K. Yamanashi, T. Sekiguchi, et al., *Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose-volume histogram analysis.* J Radiat Res, 2015. **56**(3): p. 568-76.
47. Macomber, M.W., S.R. Bowen, O. Gopan, R. Yeung, S. Apisarnthanarax, J. Zeng, et al., *Heart Dose and Outcomes in Radiation Treatment for Esophageal Cancer.* Cureus, 2018. **10**(3): p. e2378.
48. Zeng, Y.C., S. Vyas, Q. Dang, L. Schultz, S.R. Bowen, V. Shankaran, et al., *Proton therapy posterior beam approach with pencil beam scanning for esophageal cancer : Clinical outcome, dosimetry, and feasibility.* Strahlenther Onkol, 2016. **192**(12): p. 913-921.
49. Feng, H., T.T. Sio, W.G. Rule, R.S. Bhangoo, P. Lara, C.L. Patrick, et al., *Beam angle comparison for distal esophageal carcinoma patients treated with intensity-modulated proton therapy.* Journal of Applied Clinical Medical Physics, 2020. **21**(11): p. 141-152.

50. Celik, E., W. Baus, C. Baues, W. Schröder, A. Clivio, A. Fogliata, et al., *Volumetric modulated arc therapy versus intensity-modulated proton therapy in neoadjuvant irradiation of locally advanced oesophageal cancer.* Radiation Oncology, 2020. **15**(1): p. 120.
51. Warren, S., C.N. Hurt, T. Crosby, M. Partridge, and M.A. Hawkins, *Potential of Proton Therapy to Reduce Acute Hematologic Toxicity in Concurrent Chemoradiation Therapy for Esophageal Cancer.* International journal of radiation oncology, biology, physics, 2017. **99**(3): p. 729-737.
52. Warren, S., M. Partridge, A. Bolsi, A.J. Lomax, C. Hurt, T. Crosby, et al., *An Analysis of Plan Robustness for Esophageal Tumors: Comparing Volumetric Modulated Arc Therapy Plans and Spot Scanning Proton Planning.* International journal of radiation oncology, biology, physics, 2016. **95**(1): p. 199-207.
53. Lin, S.H., B.P. Hobbs, V. Verma, R.S. Tidwell, G.L. Smith, X. Lei, et al., *Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer.* J Clin Oncol, 2020: p. Jco1902503.
54. Shiraishi, Y., P. Fang, C. Xu, J. Song, S. Krishnan, E.J. Koay, et al., *Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy.* Radiother Oncol, 2018. **128**(1): p. 154-160.
55. Lin, S.H., K.W. Merrell, J. Shen, V. Verma, A.M. Correa, L. Wang, et al., *Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer.* Radiother Oncol, 2017. **123**(3): p. 376-381.
56. Chen, D., H. Menon, V. Verma, S.N. Seyedin, J.A. Ajani, W.L. Hofstetter, et al., *Results of a Phase 1/2 Trial of Chemoradiotherapy With Simultaneous Integrated Boost of Radiotherapy Dose in Unresectable Locally Advanced Esophageal Cancer.* JAMA Oncol, 2019. **5**(11): p. 1597-604.
57. DeCesaris, C.M., M. Berger, J.I. Choi, S.R. Carr, W.M. Burrows, W.F. Regine, et al., *Pathologic complete response (pCR) rates and outcomes after neoadjuvant chemoradiotherapy with proton or photon radiation for adenocarcinomas of the esophagus and gastroesophageal junction.* Journal of gastrointestinal oncology, 2020. **11**(4): p. 663-673.
58. Bhangoo, R.S., T.A. DeWees, N.Y. Yu, J.X. Ding, C. Liu, M.A. Golafshar, et al., *Acute Toxicities and Short-Term Patient Outcomes After Intensity-Modulated Proton Beam Radiation Therapy or Intensity-Modulated Photon Radiation Therapy for Esophageal Carcinoma: A Mayo Clinic Experience.* Advances in Radiation Oncology, 2020. **5**(5): p. 871-879.
59. Routman, D.M., A. Garant, S.C. Lester, C.N. Day, W.S. Harmsen, C.T. Sanheuza, et al., *A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer.* Adv Radiat Oncol, 2019. **4**(1): p. 63-69.
60. Lin, S.H., R. Komaki, Z. Liao, C. Wei, B. Myles, X. Guo, et al., *Proton beam therapy and concurrent chemotherapy for esophageal cancer.* Int J Radiat Oncol Biol Phys, 2012. **83**(3): p. e345-51.
61. Fang, P., Y. Shiraishi, V. Verma, W. Jiang, J. Song, B.P. Hobbs, et al., *Lymphocyte-Sparing Effect of Proton Therapy in Patients with Esophageal Cancer Treated with Definitive Chemoradiation.* Int J Part Ther, 2018. **4**(3): p. 23-32.
62. Takada, A., T. Nakamura, K. Takayama, C. Makita, M. Suzuki, Y. Azami, et al., *Preliminary treatment results of proton beam therapy with chemoradiotherapy for stage I-III esophageal cancer.* Cancer Med, 2016. **5**(3): p. 506-15.
63. Ishikawa, H., T. Hashimoto, T. Moriwaki, I. Hyodo, K. Hisakura, H. Terashima, et al., *Proton beam therapy combined with concurrent chemotherapy for esophageal cancer.* Anticancer Res, 2015. **35**(3): p. 1757-62.
64. Mizumoto, M., S. Sugahara, H. Nakayama, H. Hashii, A. Nakahara, H. Terashima, et al., *Clinical results of proton-beam therapy for locoregionally advanced esophageal cancer.* Strahlenther Onkol, 2010. **186**(9): p. 482-8.

65. Mizumoto, M., S. Sugahara, T. Okumura, T. Hashimoto, Y. Oshiro, N. Fukumitsu, et al., *Hyperfractionated concomitant boost proton beam therapy for esophageal carcinoma.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e601-6.
66. Ono, T., H. Wada, H. Ishikawa, H. Tamamura, and S. Tokumaru, *Clinical Results of Proton Beam Therapy for Esophageal Cancer: Multicenter Retrospective Study in Japan.* Cancers (Basel), 2019. **11**(7).
67. Ono, T., H. Wada, H. Ishikawa, H. Tamamura, and S. Tokumaru, *Proton beam therapy is a safe and effective treatment in elderly patients with esophageal squamous cell carcinoma.* Thoracic cancer, 2020. **11**(8): p. 2170-2177.
68. Ono, T., T. Nakamura, Y. Azami, H. Yamaguchi, Y. Hayashi, M. Suzuki, et al., *Clinical results of proton beam therapy for twenty older patients with esophageal cancer.* Radiol Oncol, 2015. **49**(4): p. 371-8.
69. Sato, D., A. Motegi, T. Kadota, T. Kojima, H. Bando, K. Shinmura, et al., *Therapeutic results of proton beam therapy with concurrent chemotherapy for cT1 esophageal cancer and salvage endoscopic therapy for local recurrence.* Esophagus, 2020. **17**(3): p. 305-311.
70. Hobbs, B.P., P.F. Thall, and S.H. Lin, *Bayesian Group Sequential Clinical Trial Design using Total Toxicity Burden and Progression-Free Survival.* Journal of the Royal Statistical Society. Series C, Applied statistics, 2016. **65**(2): p. 273-297.
71. *Radiotherapy dose fractionation, third edition (2019)* *https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition*.
72. Lordick, F., C. Mariette, K. Haustermans, R. Obermannová, and D. Arnold, *Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†].* Annals of Oncology, 2016. **27**: p. v50-v57.
73. Rackley, T., T. Leong, M. Foo, and T. Crosby, *Definitive Chemoradiotherapy for Oesophageal Cancer — A Promising Start on an Exciting Journey.* Clinical Oncology, 2014. **26**(9): p. 533-540.
74. Cho, O., M. Chun, S.J. Chang, Y.T. Oh, and O.K. Noh, *Prognostic Value of Severe Lymphopenia During Pelvic Concurrent Chemoradiotherapy in Cervical Cancer.* Anticancer Res, 2016. **36**(7): p. 3541-7.
75. Campian, J.L., X. Ye, M. Brock, and S.A. Grossman, *Treatment-related lymphopenia in patients with stage III non-small-cell lung cancer.* Cancer investigation, 2013. **31**(3): p. 183-188.
76. So, T.H., S.K. Chan, W.L. Chan, H. Choi, C.L. Chiang, V. Lee, et al., *Lymphopenia and Radiation Dose to Circulating Lymphocytes With Neoadjuvant Chemoradiation in Esophageal Squamous Cell Carcinoma.* Advances in Radiation Oncology, 2020.
77. *Paganetti H., Bortfeld T. (2006) Proton Therapy. In: Schlegel W., Bortfeld T., Grosu AL. (eds) New Technologies in Radiation Oncology. Medical Radiology (Radiation Oncology). Springer, Berlin, Heidelberg.*
78. Paganetti, H., *Range uncertainties in proton therapy and the role of Monte Carlo simulations.* Physics in medicine and biology, 2012. **57**(11): p. R99-R117.
79. Bert, C. and M. Durante, *Motion in radiotherapy: Particle therapy.* Physics in medicine and biology, 2011. **56**: p. R113-44.
80. Yock, A.D., R. Mohan, S. Flampouri, W. Bosch, P.A. Taylor, D. Gladstone, et al., *Robustness Analysis for External Beam Radiation Therapy Treatment Plans: Describing Uncertainty Scenarios and Reporting Their Dosimetric Consequences.* Practical Radiation Oncology, 2019. **9**(4): p. 200-207.
81. Lowe, M., A. Gosling, O. Nicholas, T. Underwood, E. Miles, Y.C. Chang, et al., *Comparing Proton to Photon Radiotherapy Plans: UK Consensus Guidance for Reporting Under Uncertainty for Clinical Trials.* Clinical Oncology, 2020.

82. Knopf, A.C., T.S. Hong, and A. Lomax, *Scanned proton radiotherapy for mobile targets-the effectiveness of re-scanning in the context of different treatment planning approaches and for different motion characteristics.* Phys Med Biol, 2011. **56**(22): p. 7257-71.
83. MacKay, R.I., *Image Guidance for Proton Therapy.* Clin Oncol (R Coll Radiol), 2018. **30**(5): p. 293-298.
84. Mori, S., A.-C. Knopf, and K. Umegaki, *Motion management in particle therapy.* Medical Physics, 2018. **45**(11): p. e994-e1010.
85. Paganetti, H., *Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer.* Phys Med Biol, 2014. **59**(22): p. R419-72.