Review Article

Particle therapy in gastrointestinal cancer—a narrative review

Matthias Mattke^

Department of Radiation Oncology, Paracelsus Medical University, SALK, Salzburg, Austria

Correspondence to: Dr. med. Matthias Mattke, MD. Department of Radiation Oncology, Paracelsus Medical University, SALK, Müllner Hauptstraße 48, 5020 Salzburg, Austria. Email: m.mattke@salk.at.

Background and Objective: Radiation therapy is one of the main pillars in the treatment of gastrointestinal (GI) cancers, especially esophageal and anorectal malignancies. The worldwide standard of care is yet an irradiation with photons. Though not commonly used, charged particles offer some physical advantages with a highly conformal dose distribution, which allows an even better sparing of organs at risk. In addition to dosimetric advantages, heavy-ion beams like carbon ions may offer an additional set of biological advantages. Because particle therapy is not standard of care, data are scarce—especially concerning the use in GI malignancies. The aim of this review is to provide a compact overview of the currently available literature.

Methods: PubMed and Web of Science databases were searched for publications on particle radiotherapy in GI cancer (e.g., proton therapy in esophageal cancer, carbon ion radiotherapy in pancreatic cancer).

Key Content and Findings: Here we present a review of the current data on particle therapy with regard to esophageal, pancreatic, hepatic and anorectal malignancies.

Conclusions: Data on particle therapy in GI cancer are scarce. Nevertheless, the current literature shows some promising results. Further clinical evidence, especially randomized trials, is crucial to augment the role of particle radiotherapy in GI cancer.

Keywords: Particle; protons; carbon ions; gastrointestinal cancer (GI cancer)

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Introduction

With advances in cancer therapy, cancer survivors are living significantly longer. Acute and chronic side effects as well as quality of life play an increasingly important role in treatment of cancer. Thus, the minimization or avoidance of side effects is—besides tumor control—one of the main goals in modern radiation therapy.

Though pretty similar in their effect on tumor cells, there are vast differences between conventional photon (X-ray) radiation and charged particles such as protons or even heavy ions. Due to their physical properties, photons have a potentially infinite range. However, the penetration depth of any kind of radiation into matter is limited by a variety of interactions. The predominantly limiting effects for photons are the photoelectric effect, the Compton effect, scattering, pair formation and nuclear reactions depending on the energy of the photons as well as the material of the irradiated tissue. An exponential weakening begins from the moment the radiation hits matter; therefore, the main energy output already takes place in the entry area of the beam. In contrast, the deceleration of particle radiation (which, due to its physical properties has a finite range) happens through interactions with atomic nuclei and electrons of the atomic shell. The probability of interaction increases with decreasing velocity of the particle. Since ions of the same energy are used in medical applications, the main energy release takes place at a defined point, the so-called Bragg peak. This point of maximum

^ ORCID: 0000-0001-5057-6065.

Table 1 The search strategy summary

Items	Specification
Date of search	2023/08/13
Databases and other sources searched	PubMed, Web of Science
Search terms used	Protons, carbon ions, particle therapy, esophageal cancer, anorectal cancer, rectal cancer, anal cancer, pancreatic cancer, liver cancer, hepatocellular carcinoma, neoadjuvant, definitive, preoperative, postoperative, radiotherapy, irradiation
Timeframe	1990–2023
Inclusion and exclusion criteria	Inclusion of full text publications in English; exclusion of case reports
Selection	All articles were analysed for suitability by M.M.

energy release can be modified via the initial particle energy (velocity). Thus, a precise energy deposition in the tumor tissue with simultaneously very low energy release in the surrounding (normal) tissue is possible. Thus, very steep dose gradients and often significantly better dosimetric protection of organs at risk can be achieved. The biological rationale for heavy ions in radiation therapy is based on their higher energy output compared to protons or photons. This higher energy output results in a significantly increased ionization density, leading to a greater probability of interaction with DNA. As a result, heavy ions exhibit an increased relative biological effectiveness (RBE) compared to photon irradiation. This advantage seems particularly beneficial in treating hypoxic tissues that are resistant to conventional photon radiation, as heavy ions have more direct interactions with DNA and less dependence on radical formation based on oxygen. This is why heavy ions are used for the radiotherapy of normally radioresistant tumors.

While this sounds beneficial and easy in theory, the high precision may trigger other problems, especially in moving targets/organs like the luminal gastrointestinal (GI) system. The precision of particle radiotherapy can be heavily influenced by air in the beam direction and is prone to dose inhomogeneities, especially in tissues surrounded by structures with changing fillings of gases. Thus, the robustness of the particle-radiotherapy plan (i.e., if the dose can be applied as planned in every fraction) will be influenced much more profoundly by anatomical changes than photon radiation. Moreover, dosimetric advantages do not necessarily translate into clinically meaningful benefits.

Whilst there are ample dosimetric studies concerning the use of particle therapy in GI-cancers, clinical data are still rather scarce. Several review articles have been published, the latest in 2022 (1). Regarding randomized data only one trial concerning proton therapy in esophageal cancer has been published so far (2). In the following parts we will discuss the current literature on particle therapy for esophageal, pancreatic, liver and anorectal cancer. I present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-757/rc).

Methods

Publications (up to August 2023) in English language were searched in PubMed and Web of Science. After analysis, the references of the selected publications were also searched for further relevant publications. As specific data are scarce, no minimum of patients in the according publications could be defined. Nevertheless, case reports were excluded from review (*Table 1*).

Esophageal cancer

Depending on the tumor staging, chemoradiotherapy is one of the standard treatments in esophageal cancer. Nevertheless, the incidence of late cardiopulmonary toxicities grade 3 and higher was found to be 29–45% in several clinical studies (3,4). The use of intensity modulated radiotherapy (IMRT) can reduce the heart dose with a significant sparing of the right coronary artery (5) or several other substructures (6) which results in a significantly reduced incidence of cardiac deaths compared to three-dimensional conformal radiotherapy (3D-CRT) (7). Taking abovementioned possible advantages of particle therapy into consideration, an even better sparing of organs at risk and a reduction of side effects seems possible, using charged

Table 2 Particle studies concerning esophageal cancer

Study	Modality	Number	Median dose	Local control (%)	Survival (%)
Koyama *et al.* 2003	Photon/proton; proton	30 (superficial n=13; advanced n=17)	Superficial 77.7 Gy (RBE); advanced 80.7 Gy (RBE)	10-year: superficial, 100; advanced, 78.3	DSS 10-year: superficial, 87.5; advanced, 38.1
Sugahara *et al.* 2005	Photon/proton; proton	46 (photon/proton n=40; proton n=6)	48 Gy photon + 31.7 Gy (RBE) proton; 82 Gy (RBE) proton only	5-year: T1, 83; T2–T4, 29	OS 5-year: all, 34; T1, 55; T2–T4, 13
Mizumoto *et al.* 2010	Photon/proton; proton	51 (photon/proton n=33; proton n=18)	46 Gy photon + 36 Gy (RBE) proton; 79 Gy (RBE) proton only	5-year: 38	OS 5-year: 21.1
Ishikawa *et al.* 2018	Proton + chemotherapy (cisplatin/5-FU)	67	60 Gy (RBE)	3-year: 73	OS 4-year: stadium I, 96; stadium II, 73; stadium III, 40
Lin *et al.* 2020	Photon/proton (randomized)	107	50.4 Gy (RBE)	3-year PFS: IMRT, 44.5; proton, 44.5	3-year: IMRT, 50.8; proton, 51.2

RBE, relative biological effectiveness; DSS, disease-specific survival; OS, overall survival; 5-FU, 5-fluorouracil; PFS, progression-free survival; IMRT, intensity modulated radiotherapy.

particles. Also, the lungs can be spared significantly better, especially considering widespread low radiation doses. The first clinical studies to include proton therapy (as a boost in combination with a conventional therapy or proton only therapy) in esophageal cancer were performed in Japan and were mostly dose escalation studies with doses up to 80.4 Gy. Good disease specific survival rates of around 90% for superficial and around 35% for advanced lesions after 5 to 10 years could be found (8-10). Nevertheless, it needs to be mentioned, that a higher risk for esophageal ulcers was observed with doses >80 Gy in one study, which is not necessarily surprising (11). Furthermore, it needs to be discussed, that patients were treated with radiotherapy only. At least in comparison to photons, combined radiochemotherapy is superior to radiotherapy alone (12).

Even though radiochemotherapy has been a standard treatment for many years in esophageal cancer, data for the combination of a systemic therapy with particle radiotherapy are scarce.

Ishikawa *et al.* reported on 67 patients with squamous cell carcinoma who received 60 Gy (RBE) in 30 fractions (13). The 4-year overall survival (OS) rates for stages I, II and III were 96%, 73% and 40%, respectively.

The only prospective randomized study concerning neoadjuvant proton therapy in esophageal cancer was performed at MD Anderson Cancer Center (2). A total of 107 patients who received concurrent radiochemotherapy were randomized between proton therapy and IMRT with the same prescription dose of 50.4 Gy. There was no difference between the two groups in the 3-year OS and progression-free survival (PFS) rates. A significant difference could be determined in the total toxicity burden (TTB) which was also the primary endpoint of the trial. The TTB was 2.3 times higher in the IMRT arm. Furthermore, postoperative complications were 7.6 times higher in the IMRT arm. It needs to be mentioned, that the decrease in TTB in the proton arm was mainly driven by the decrease in postoperative complications. No significant differences could be determined when the individual adverse events were compared and analyzed. An overview of the study results can be found in *Table 2*.

The question may arise, why no dose escalation in this neoadjuvant setting was performed if this seems to be feasible as some of the abovementioned studies have shown. The reason is rather simple. Particle therapy may have dosimetric advantages concerning organs at risk that are close to the target volume. The main problem regarding radiation toxicity in esophageal irradiation is the esophagus itself, which in this particular case is target and organ at risk at the same time. If dose escalation creates significant side effects in the esophagus itself, consequent surgery may be compromised, delayed or in the worst case impossible.

Pancreatic cancer

Pancreatic cancer remains an oncological diagnosis with a grim prognosis as most patients present with metastatic disease and only about 10–20% are eligible for resection,

Table 3 Particle studies concerning pancreatic cancer

Study	Modality	Number	Median dose, Gy (RBE)	Local control (%)	Overall survival (%)
Hong *et al.* 2014	Proton	50	25 (5 fractions)	3-year: 84	2-year: 42
Terashima *et al.* 2012	Proton	50	50–70.2	1-year: 81.7	1-year: 76.8
Liermann *et al.* 2022	Carbon	13	48	1-year: 87.5	2-year: 25

RBE, relative biological effectiveness.

which is the only curative treatment option. However, even more than 80% of patients who undergo surgery die due to local recurrence or metastatic disease (14,15).

The standard postoperative therapy includes chemotherapy, the role of concomitant radiochemotherapy is still subject to discussion though several studies described a possible benefit for local control (LC) when performing radiochemotherapy (16,17). Being surrounded by many radiosensitive organs at risk, the steep dose gradients of particle therapy are preferable over conventional photon therapy. Several plan comparison studies were able to show dosimetric advantages of proton therapy over photon therapy. For example, Thompson *et al.* were able to show reductions in the low and moderate doses to the stomach and the small bowel with the best results being achieved while using a pencil beam scanning technique (18). In a postoperative setting, Nichols *et al.* were able to show drastic dose reductions in the small bowel and stomach using protons (19).

Clinical data are scarce with no randomized trials comparing particle therapy to conventional radiotherapy. The existing data are limited to rather small, mostly retrospective, case series. For preoperative radiochemotherapy the larges cohort with 50 patients was reviewed by Hong *et al.* (20). Thirty-seven patients underwent pancreaticoduodenectomy. LC was achieved in 84% of patients with a 4.1% rate of grade 3 toxicity and 0% of grade 4 or 5 toxicity.

The main application for particle therapy may be unresectable pancreatic carcinomas, in which dose escalation may be of advantage considering local tumor control. Combined approaches with particle therapy after neoadjuvant chemotherapy also seem possible. Albeit being a promising field of research data are also scarce. For unresectable pancreatic carcinoma a larger cohort of 50 patients was reviewed by Terashima *et al.* (21). The 1-year LC rate was 81.7% with a rate of late toxicity grade 3+ of 10%. Ami *et al.* recently reported retrospectively on 200 patients who were treated with protons [67.5 Gy (RBE)] with or without chemotherapy. LC rate after 2 years was 44.3% and OS after 2 years was 35.4% (22).

Concerning a definitive treatment in locally recurrent pancreatic cancer, a collective of 13 patients was irradiated with carbon ions at Heidelberg. Though most patients developed distant metastases, the estimated 1-year LC and locoregional control rates were 87.5% and 75%, respectively. One patient suffered from G3 toxicity (GI bleeding). Apart from that no further higher-grade acute or late toxicities were observed (23). *Table 3* contains an overview of the study results.

Generally speaking, because of the surrounding bowels, dose uncertainties are a relevant point concerning particle therapy. Due to the bowel movement and changing filling (especially changes in gas load), significant changes in anatomy and therefore dose distribution can occur, even between two fractions and close monitoring under radiotherapy is necessary. So far, the clinical data imply that particle therapy for pancreatic cancer is safe and effective, though larger analyses or even randomized studies could augment the use of particle therapy in the treatment of pancreatic cancer.

Liver cancer

In 2020 primary liver cancer was the sixth most common neoplasm and the third leading cause of cancer-related death worldwide. Rates of incidence as well as mortality are 2 to 3 times higher among men. Hepatocellular carcinoma (HCC) account for the majority of liver cancer cases (75–85%) (24).

Still, surgical resection or orthotopic liver transplantation (OLT) are the therapies of choice with a 5-year survival up to 60–70% (25). Nevertheless, only a minority of patients are suitable for resection or OLT due to medical or anatomical reasons. Other local therapies like transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) may be used in a palliative setting. Radiation therapy has played a minor role historically, as the dose required for sufficient tumor control surpasses the dose tolerance of the liver, especially as those tumors mostly occur in damaged livers with impaired function (26). The

technical improvements in IMRT and stereotactic body radiotherapy (SBRT) concerning dose conformity have established new possibilities for photon radiotherapy of the liver (27). Nevertheless, the cumulative entry and exit doses of conventional radiotherapy may still exceed the dose tolerance of the healthy liver tissue. Because of the abovementioned properties with superior target conformation, particle therapy may be of particular interest in the treatment of liver tumors (28,29).

Several studies have been published on the use of particle therapy in HCC, especially for the use of protons. Kawashima *et al.* performed one of the first prospective trials, which included 30 patients with solitary tumors and liver cirrhosis (30). Patients had a median tumor size of 4.5 cm and were treated with 76 Gy (RBE) in 20 fractions. During the median follow-up of 31 months, only one patient experienced a local recurrence and the 2-year OS was 66% with minimal acute toxicity. In another prospective trial 51 patients with a median tumor size of 2.8 cm and Child-Pugh class A or B cirrhosis were treated with 66 Gy (RBE) in 10 fractions (31). The 5-year LC rate was 87.8% and OS was 38.7%, in patients with Child-Pugh class A cirrhosis OS was 42.1%. Patients experienced only minor toxicities. Bush *et al.* reported on 76 patients of which 54% were outside of Milan criteria, 24% had Child-Pugh class C cirrhosis and 16% had a model of end-stage liver disease (MELD) score >15 (32). Patients received 63 Gy (RBE) in 25 fractions. The median PFS was 36 months with a 3-year PFS rate of 60% for patients within the Milan criteria. Median time to failure was 18 months with a LC rate of 80%. Acute toxicity was again minimal. The same group performed an interesting randomized trial comparing TACE with proton therapy [70.2 Gy (RBE) in 15 fractions] (33). Total number of hospitalization days within 30 days of the procedures (62 *vs.* 2, P<0.001) as well as total hospitalization days (166 *vs.* 24, P<0.001) were in favor of proton therapy. There was no difference concerning median survival (32 months) or 2-year OS (65% *vs.* 68%, P=0.8). Nevertheless, there was a significantly better 2-year LC and PFS in patients who received proton therapy. Komatsu *et al.* reported on 343 patients treated with protons and carbon-ions (34). Dose and fractionation schemes were rather widespread [52.8–84.0 Gy (RBE)/4–38 fractions for protons; 52.8–76.0/4–20 for carbon ions]. LC rate after 5 years was reported to be 90.8% and OS 38.2%. Three patients experienced grade 3 toxicities. Radiation induced hepatic dysfunction was found in four patients.

Concerning carbon ion therapy, 24 patients were treated in a phase I/II trial by Kato *et al.* (35). Total dose was 49.5–79.5 Gy (RBE) in 15 fractions. LC rate after 3 years was 81% and OS after 5 years 25%. No severe liver injury was observed. Shibuya et a retrospectively reported on 174 patients treated in ultra-hypofractionated settings with either 52.8 Gy (RBE)/4 fractions, 60.0/4 or 48/2, respectively (36). LC rate and OS at 3 years were 87.7% and 73.3%, respectively. The rate of grade 3–4 toxicities was 5.7%.

Hiroshima *et al.* retrospectively analyzed 58 patients with Child B cirrhosis who underwent carbon-ion therapy with doses between 45 and 60 Gy (RBE) in 2 to 4 fractions (37). LC rate after 2 years was 96.4% and OS 46%. Another retrospective analysis was published by Tomizawa *et al.* (38). In a recurrent situation, 41 patients were treated with 52.8–60.0 Gy (RBE) in 4–12 fractions. The 2-year OS and LC rate were 83.0% and 56%, respectively.

Regarding the comparison between carbon-ion therapy and TACE, Shiba *et al.* published the results of a propensity score matching study in 2019 (39). After 3 years, carbon ion therapy was significantly better in OS (88% *vs.* 58%; P<0.05), LC rate (80% *vs.* 26%; P<0.01) and PFS (51% *vs.* 15%; P<0.05).

An overview of the study results can be found in *Table 4*.

In summary, the level of evidence for particle therapy in HCC is much better than in other GI-tumors with encouraging results concerning OS and LC and low rates of side effects. Nevertheless, most studies are retrospective and further (especially randomized) evidence is needed.

Anorectal cancer

Radiochemotherapy is traditionally one of the cornerstones in the treatment of anorectal cancer. As LC rates are rather high in anorectal cancer, the main rationale for particle therapy may be the minimization of side effects or the treatment of local relapses.

Dosimetric studies were able to show better sparing of the organs at risk (OARs) while using proton therapy (40-42).

Clinical data go back to 1977 when Suit *et al.* reported on patients with different types of cancer. Patients with anorectal cancer were included and the treatment was tolerated well (43). Jeans *et al.* reported on the use of a neoadjuvant short-term proton therapy, which was tolerated very well with no side effects > grade 2 (44). The only comparative study was conducted by Mohiuddin *et al.* (45). Two hundred and eight patients with anal squamous cell carcinoma who received either proton or photon therapy were compared. There was no difference in LC or toxicity;

Table 4 Particle studies concerning liver cancer

Study	Modality	Number	Median dose, Gy (RBE)	Local control (%)	Overall survival (%)
Kawashima *et al.* 2005	Proton	30	76	2-year PFS: 96	2-year: 66
Fukumitsu *et al* 2009	Proton	51	66	5-year: 87.8	5-year: 38.7
Bush *et al.* 2011	Proton	76	63	3-year PFS: within Milan, 60; outside Milan, 22	3-year: with liver-transplant, 70; without liver-transplant, 11
Komatsu *et al.* 2011	Proton/carbon	343	52.8–84	5-year: 90.8	5-year: 38.2
Kato *et al.* 2004	Carbon	24	49.5–79.5	3-year: 81	5-year: 25
Shibuya *et al.* 2018	Carbon	174	48–60	3-year: 81	3-year: 73.3
Hiroshima *et al.* 2023	Carbon	58	45–52.8	2-year: 96.4	2-year: 46
Tomizawa *et al.* 2023	Carbon	41	52.8–60 (repeated)	2-year: after second RT, 83	2-year: after first RT, 87.8; after second RT, 56

RBE, relative biological effectiveness; PFS, progression-free survival; RT, radiotherapy.

Table 5 Particle studies concerning anorectal cancer

Study	Modality	Number	Median dose, Gy (RBE)	Local control (%)	Overall survival (%)
Mohiuddin *et al.* 2021	Photon; proton	208 (photon n=150; proton n=58)	50.4–54	2-year: photon, 88; proton, 91; n.s.	n/a; no difference in toxicity
Yamada *et al.* 2021	Carbon	235	67.2–73.6	5-year: 88	5-year: 46
Hiroshima *et al.* 2021	Proton	12	72	3-year: 80.2	3-year: 73.8

RBE, relative biological effectiveness; n.s., not significant; n/a, not applicable.

proton therapy was dosimetrically superior compared to the photon therapy. In 2011, Lee *et al.* reported on 67 patients with locally recurrent rectal cancer. It was noted that in the four patients who received protons as a part of the concurrent chemoradiation therapy, higher doses could be prescribed even with OARs in close proximity (46).

Meanwhile, the therapy regimen has changed significantly with total neoadjuvant therapy (TNT) offering the chance of better disease-free survival and lower risk of distant metastasis (47) in rectal cancer. A randomized study from Sweden (PRORECT) is comparing preoperative short-course radiotherapy with protons to photons as part of a TNT approach. So far only dosimetric results have been published, showing significantly less dose in the organs at risk using protons (48).

This leaves the treatment of locally recurrent anorectal cancer as a field of special interest regarding the use of particle therapy. Nevertheless, only little data are available let alone randomized data. A large collective consists of 235 patients that were treated in a phase I/II dose escalation study with carbon ions in Japan. Total dose ranged from 67.2 to 73.6 Gy (RBE). Patients were treated over the course of 4 weeks with a low number of adverse events (one GI ulcer grade 3 was described, no further acute reactions > grade 2). The overall LC rate was 90% at 3 years and 88% at 5 years (49).

Concerning the use of protons in recurrent anorectal cancer, Hiroshima *et al.* reported on 12 patients, who received a proton therapy with a 3-year LC rate of 80.2% (50).

With good LC rates and low side effects, reirradiation to the pelvis with particles seems to be a treatment alternative worth considering in patients with recurrent anorectal cancer. Nevertheless, randomized trials are urgently needed as the level of evidence is still rather low.

The results of the studies are summarized in *Table 5*.

Conclusions

The use of particle therapy in GI cancer seems promising, though clinical data are scarce for most tumor entities. Dosimetric analyses were able to show clear advantages over conventional photon therapy, which can result in lower

toxicity rates. The few available clinical trials suggest that particle therapy is safe and effective in the therapy of GI cancers. Solid clinical data are only available for HCC; yet randomized phase III trials are still lacking. Nevertheless, particle therapy is considerably more laborious in terms of work and cost. This can only be justified, if the dosimetric advantages translate into meaningful clinical advantages—either improved tumor control or reduced toxicity. Both have not been shown yet for most GI indications. Further clinical evidence, especially randomized trials, is crucial to augment the role of particle therapy in the treatment of GI cancer.

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