SA–CME Information

PROTON THERAPY FOR COLORECTAL CANCER

Description

Based on current standards, colon cancer is treated with surgical resection and chemotherapy, and rectal cancer is treated with preoperative radiotherapy. This review of the literature suggests the potential for improved local control and reduced toxicity when treating colorectal cancer with proton therapy compared to the current treatment paradigms. Additionally, surgery and ablative techniques have traditionally been used to treat metastatic colorectal cancer. This review discusses how proton therapy could offer an alternative approach to reduce toxicity and act in lieu of surgery in the metastatic setting.

Learning Objectives

After completing this activity, participants will be able to:

1. Evaluate dosimetric data and case reports supporting use of proton therapy for treatment of colorectal cancer.
2. Analyze role of proton therapy for treatment of oligometastatic colorectal cancer.

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Proton therapy for colorectal cancer

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Ever since the first proton beam therapy (PBT) treatment in 1954 at University of California, Berkley, the use of PBT worldwide has rapidly increased.[1] Due to the depth-dose characteristics of protons that allow for steep fall-off just distal to the tumor target, PBT can reduce unnecessary radiation dose to nearby normal tissues and allow for safer dose escalation in select clinical scenarios. Superior normal tissue avoidance can lead to reductions in acute and late toxicities, safe dose escalation can lead to improved local control, and the combination of both factors has the potential to impact overall survival (OS).

Early data have suggested that PBT led to improved clinical outcomes in the treatment of various pediatric cancers, ocular melanomas, sarcomas of the paravertebral region, and brain tumors when compared with traditional photon-based radiation.[2] Historically, fewer studies evaluated the utility of PBT in the treatment of gastrointestinal (GI) malignancies; however, retrospective studies in the setting of gastroesophageal cancer and pancreatic cancer show that preoperative PBT may reduce postoperative complications and definitive PBT may improve outcomes for those with unresectable disease.[3-6] Even fewer studies have evaluated the role of PBT in the primary or neoadjuvant treatment of colorectal cancer (CRC), but there have been published clinical outcomes in the treatment of recurrent disease as well as liver metastases. The aim of this review is to discuss the existing dosimetric and clinical data for PBT in the treatment of patients with CRC.

The Role of Radiation

Although colorectal cancer is often discussed as a single entity, colon and rectal cancer are drastically different in their clinical management. While colon cancer is treated with surgical resection and adjuvant chemotherapy for high-risk patients, radiation therapy is a standard component of preoperative treatment of rectal cancer given the higher risk of local recurrence in the pelvis (National Comprehensive Cancer Network).[7] Preoperative long-course chemoradiation or short-course radiation therapy are standard-of-care strategies for improving local-regional control in stage II and III rectal cancer. Preoperative radiation therapy reduces the risk of local recurrence,[8] which can be extremely morbid and difficult to salvage. However, radiation therapy is not without potential long-term risks, which include anastomotic leak, fistula formation, bowel adhesions/narrowing predisposing to obstruction, bladder scarring, erectile dysfunction, dyspareunia, pelvic insufficiency fracture and secondary malignancy.[9] As such, recent efforts have been made to reduce toxicity while maintaining excellent control and survival rates. One strategy has been to omit radiation therapy in patients with more favorable disease characteristics on advanced magnetic resonance imaging (MRI) who may not need it.[10] A recently completed trial evaluated omitting preoperative radiation after a good clinical response to induction chemotherapy (NCT01515787). Another strategy involves delivering radiation therapy in a more conformal way. RTOG 0822 evaluated preoperative intensity-modulated radiation therapy (IMRT) and failed to show decreased toxicity when compared to historic controls treated with a 3-dimensional (3D) conformal technique.[11] This trial was difficult to evaluate, however, as concurrent oxaliplatin was used with the IMRT.

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In the era of neoadjuvant therapy and total mesorectal excision, although local control rates for locally advanced rectal cancer are > 90%, distant metastases occur in approximately 30% of patients.[8] Additionally, 25% of all patients with colorectal cancer are metastatic at diagnosis, with the liver being the most common site.[12] For patients with oligometastatic disease, multimodality, definitive treatment can yield long-term survivorship.[13] Resection of liver metastases in combination with more effective chemotherapy has increased the median survival to 20 months and the 10-year OS to 20% to 25%.[14] However, as many patients are not surgical candidates, interest is growing in the use of radiation therapy or other ablative modalities in the treatment of liver metastases. Using advanced radiation techniques to achieve dose escalation is of particular interest because of studies showing a correlation between higher biologically effective dose (BED) and prolonged survival.[15,16]

Finally, for a small subset of patients, local recurrence of rectal cancer presents a unique clinical challenge. While surgical salvage is preferred, this approach can be morbid and technically challenging. As most recurrences arise within a previously irradiated field, preoperative or definitive reirradiation options are limited. Hyperfractionated, accelerated schedules have been shown to be safe,[17] although more conformal techniques such as stereotactic body radiation (SBRT) or particle therapy may further improve the therapeutic ratio for these patients.

The Rationale for Protons

PBT is a nuanced radiation therapy technique that has the potential to greatly reduce toxicity in the settings of locally advanced rectal cancer as well as oligometastatic colorectal cancer. Due to the favorable physical properties of the proton beam, the unnecessary exposure of normal tissue to radiation can be reduced. The proton is a positively charged particle given energy via acceleration in a cyclotron (or synchrotron), which then enters the patient's body at a brisk speed, depositing very little dose. The dose absorbed by the body increases as the proton slows down at greater depth until the absorbed dose rises to an abrupt peak called the Bragg peak. The proton beam can be programmed such that the Bragg peak occurs exactly within the tumor site. After the Bragg peak, there is a steep dose fall-off, which eliminates unnecessary dose distal to the intended tumor target.[18]

These physical properties offer potential acute and late toxicity advantages in the treatment of localized rectal cancer where sparing of the small bowel, femoral heads, bladder, genitalia, and other abdominal and pelvic structures is desired. In the metastatic colorectal cancer setting, PBT has the potential to spare healthy, nontarget liver and lung tissue from radiation allowing for dose escalation while respecting normal tissue dose constraints. This is particularly important when treating large or multiple liver metastases as the risk for radiation-induced liver disease (RILD) may be greater with photon-based techniques.

Dosimetric Data

Treatment planning studies have nicely illustrated the ability of PBT to reduce unnecessary dose to normal tissues adjacent to the tumor targets, and these dosimetric benefits are thought to translate to acute and late toxicity reduction. For localized rectal cancer, several dosimetric analyses have compared PBT to photon radiation for pelvic radiation. In these studies, PBT was significantly superior in reducing V5Gy, V10Gy, V15Gy, and V20Gy to bone marrow; V10Gy and V20Gy to small bowel; and V40Gy to the bladder.[19-23] Others have found better conformality indices with protons and sparing of male genitalia with proton compared to photon therapy.[20] There is also some suggestion that proton dosimetry may be particularly better for larger tumors.[2]

This evidence suggests that long-term toxicity risk may be significantly reduced for patients undergoing pelvic radiation for locally advanced rectal cancer. In particular, bone marrow sparing can be highly advantageous as patients often undergo myelosuppressive chemotherapy. Being able to preserve marrow progenitors enables better tolerance to curative intent treatment, and the bone marrow is one organ where low doses matter. Lower V10 to the pelvic bone marrow has been associated with lower rates of significant cytopenia for patients being treated with pelvic radiation for anal cancer.[24] Preserving bone marrow function is particularly important for patients with locally advanced or metastatic rectal cancer who inevitably require long courses of cytotoxic systemic therapy.

Treatment planning studies have also shown dosimetric advantages of PBT over photon therapy in the oligometastatic setting as well. Radiation is playing an increasing role in the treatment of inoperable liver metastases. However, the low-dose bath to the rest of the liver can place the patient at risk for liver dysfunction and injury. Recent dosimetric analyses show that PBT can reduce the mean liver dose by more than half, from 20Gy to 9Gy, and reduce the V15Gy to the liver. This ability to achieve established dose constraints more easily allows for the delivery of the full intended ablative prescription dose for optimal tumor control, 90% for PBT vs only 20% with photon therapy.[25] As such, for these patients PBT may offer a toxicity and control benefit over photon therapy. Overall, dosimetric data for PBT are encouraging, although clinical outcomes are needed to ensure dosimetric benefits translate to meaningful reductions in toxicity and/or gains in tumor control.

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Clinical Outcomes

In general, published clinical outcomes for the use of PBT in the treatment of CRC are sparse. In the localized rectal cancer setting, most of the clinical data produced to date come from the salvage or reirradiation setting. In 2014, Berman published a study on 7 patients with locally recurrent rectal cancer who received reirradiation with PBT, to an average total cumulative dose of 109.8 gray relative biological effectiveness (Gy [RBE]).[26] Three patients experienced acute grade 3 toxicity, and 3 patients experienced late grade 4 toxicity at a median follow-up of 19.4 months. Out of the 7 patients, 4 were alive at the time of analysis. When compared to photon plans, PBT reduced small bowel and femur dose. The study concluded that PBT is clinically feasible and showed dosimetric improvements over IMRT when treating locally recurrent rectal cancer. In 2018, Ogi et al published a retrospective study on 23 patients who received PBT (up to 70 Gy [RBE]) for salvage reirradiation of locally recurrent rectal cancer.[27] Of these 23 patients, the grade 3 toxicity at 2.25 years after salvage was only 13% with an in-field local control rate that was moderate at 57%. In 2019, Kawamura et al published a report on 4 patients who received PBT after debulking surgery for locally recurring rectal cancer.[28] One patient died of lung metastasis after 2 years, 2 died of lymph node metastasis after 11 and 31 months, and one is alive without recurrence after 43 months. Thus, reirradiation with protons in the recurrent setting is largely considered feasible. Overall, however, the long-term outcomes for protons in this setting are sparse and there are no direct published comparisons to patients having received photon-based radiation. Furthermore, there are currently no published reports evaluating the use of PBT in the upfront treatment of locally advanced rectal cancer.

Compared with localized CRC, much more data have been published describing the use of PBT in the treatment of oligometastatic liver disease, including some prospective trials. One report discussed 5 patients with bilateral liver metastases treated with PBT.[29] These patients were planned to undergo a staged resection to allow liver hypertrophy and functional reserve between hepatectomies, but they did not have adequate hypertrophy to undergo the second stage of the operation. Using PBT, however, where the bulk of the normal liver can be spared, these investigators were able to treat all remaining disease to a BED of > 89.6 Gy (RBE) to the tumor and achieve tumor control in 4 out of 5 patients. Although this series was small, 40% of patients were without evidence of disease following treatment without any major toxicity. As such, proton therapy appears to be a feasible alternative for select patients with high burdens of liver disease who decline or are not amenable to surgery or may be combined with surgery or other ablative techniques in a multimodality approach. Hong et al recently published a single-arm phase II study on 89 patients who had received 30 to 50 gray-equivalent (GyE) proton-based stereotactic body radiation therapy (SBRT) to liver metastases, the majority of which were from CRC.[30] One-year local control was 71.9%, and 3-year local control was 61.2%. Grade 3 to 5 toxicity was not observed in these patients, and the patients had a median survival time of 18.1 months. Lastly, in 2019, Kang et al published a phase I study on the maximum tolerated dose of proton SBRT for liver metastases on 9 patients with liver lesions < 5 cm, and with no lesions within 2 cm of the GI tract. Patients did not experience dose-limiting toxicity, and dose escalation was possible without reaching maximum tolerated dose. In one patient, within 90 days of treatment, a grade 1 skin hyperpigmentation was noted. Two patients had local recurrence, and patients were treated with proton SBRT again. Recently, a consensus report emerged regarding the advantages and scenarios of PBT in treating CRC liver metastases, which will be valuable to the radiation therapy community as they consider PBT going forward.[31]

Future Directions

Currently, one ongoing clinical trial is evaluating PBT with concurrent chemotherapy for previously irradiated recurrent rectal cancer, and 2 ongoing clinical trials are exploring PBT for metastatic CRC—all led by Korean centers. A single-arm prospective study aims to treat previously irradiated, locally recurrent rectal cancer with 70.4 Gy (RBE) delivered in 16 fractions to the gross tumor volume and 44.8 Gy (RBE) in 16 fractions with the clinical target volume with concurrent capecitabine and with or without resection and spacer insertion. (A spacer is an injected degradable hydrogel that pushes structures such as the rectum in the case of re-irradiation away from normal tissues to reduce toxicity and is being explored in both the genitourinary and GI radiation therapy settings [NCT03098108].) In a phase II study of treating CRC lung metastasis, the prescription dose given is 72 Gy (RBE) in 15 fractions. The main aim is to evaluate the 3-year local control rate. Three-year survival rate and 3-year disease free survival rates are also being assessed to evaluate whether PBT offers better survival outcomes when compared to surgery (NCT03566355). In a phase II study of treating liver metastasis of colorectal adenocarcinoma, the main aim is to evaluate the 2-year local control rate. Similar to the first trial, the same regimen of 72 Gy (RBE) in 15 fractions is being used, and 5-year survival rates and 5-year disease free survival rates are listed as secondary endpoints to evaluate whether PBT offers better survival outcomes when compared with surgery, as PBT is a noninvasive procedure

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(NCT03577665). However, there is still an urgent need for more clinical trials to demonstrate whether PBT has an impact on overall survival of patients with CRC. There is a similar need for clinical trials comparing PBT to photon therapy to evaluate toxicity levels, dose escalations, and local control rates. An ongoing cooperative group trial randomizing PBT with photon-based radiation for hepatocellular carcinoma may set the stage for such phase III trials for CRC in the future (NCT03186898).

Limitations of PBT for CRC

As the radiation community seeks to leverage advanced technologies to find novel solutions for challenging clinical scenarios, it is important to recognize some of the currently limiting factors. Protons have thus far shown the largest benefit in the treatment of tumors requiring high doses delivered to tumor targets directly adjacent to radiosensitive critical structures. Notable examples include chordoma and chondrosarcoma.[32] Additionally, protons can achieve less integral body dose by minimizing low radiation dose in the beam path, which makes it potentially advantageous in reducing the risk of long-term side effects such as secondary malignancy, and neurocognitive and endocrine toxicities in the pediatric population.[33] Not much enthusiasm exists for the use of PBT in the neoadjuvant treatment of locally advanced, resectable rectal cancer partially because the tumor arises from within, rather than adjacent to, a radiosensitive luminal GI organ. Additionally, the need to treat the entire mesorectum and adjacent nodal basins necessitates a large clinical target volume that expressly overlaps with pelvic organs such as the bladder, bowel and bones. While the treatment planning studies described above show significant dose reduction, bowel and bladder toxicity is mostly due to high-dose exposure within the target area rather than low-dose scatter to adjacent normal tissues. Bone marrow is a potential exception and is one example where low dose matters. Young patients at higher risk for secondary malignancies and patients who have received prior radiation to the intended field are two other potential exceptions.

Additionally, some physical and biological properties of PBT are incompletely understood. Even though linear energy transfer (LET) and RBE are known to drastically rise at the very distal edge of the spread-out Bragg peak, conventional treatment planning systems implement standard RBE corrections uniformly across the beam. This means the RBE can be 2 to 3 times higher than prescribed and has grave potential implications should the beam's edge end just adjacent to a critical organ. This has been well described in the pediatric central nervous system literature.[34] The location of CRC targets in and around organs that have considerable inter- and intrafractional variability of positioning due to the presence of bowel contents and gas further add to this uncertainty. The stopping power of protons varies widely between tissue and air, and the presence of rectal gas can increase the range of the proton beam leading to undercoverage of the target and/or overdoing nearly critical structures.[35]

There are ongoing innovations to help improve PBT delivery. Currently, spot sizes, the size of the proton beamlets used to treat, are being reduced. With further reduction, more precise sculpting of proton dose delivery will be enabled. Additionally, new techniques such as dual-energy CT (DECT) can reduce the stopping power uncertainty with protons by as much as 50%.[36-41] Reducing this uncertainty will help to further reduce dose and spare normal tissue. Also, more experience with beam angling to optimize treatment positioning will help to perfect treatment planning. Improvements in robust optimization and evaluation will allow for better confidence in PBT treatment, and there is work ongoing to explore LET- or RBE-based optimization strategies.[42-44] Finally, advances in motion management for CRC tumors at sites such as the lung and liver where breathing can cause the tumor to move are being developed to minimize the interplay effect and ensure tumor coverage and organ at risk sparing during spot painting.[45-46]

Conclusion

With the increased use of PBT to treat various malignancies, there is renewed interest in its application in the treatment of CRC due to the location of disease and the desire to reduce toxicity from a multimodality treatment approach. In the setting of localized rectal cancer, PBT spares bone marrow, small bowel, femoral heads, and abdominopelvic structures from unnecessary radiation exposure, which may allow patients to tolerate chemotherapy or other treatment modalities. In the setting of oligometastatic disease, PBT can preserve organ function and allow for dose escalation, which has been shown to correlate with control. Numerous small series have been published but are primarily limited to cases of reirradiation or salvage in the localized rectal cancer setting. More robust data show the promise of PBT in the treatment of CRC liver metastasis. However, large, randomized clinical trials are needed to validate the efficacy and safety of PBT in treatment of CRC, particularly in the upfront setting with resectable disease.

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