

# Proton therapy for gastrointestinal cancers

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**Abstract:** Proton beam therapy provides an opportunity to deliver ionizing radiation with improved dose conformity. It has gained popularity as a means of more localized radiation delivery. However, proton therapy data are still lacking, as there are still relatively few proton treatment centers worldwide. This paucity of data is particularly evident in gastrointestinal (GI) cancers. Most GI cancers are located in close proximity to or abut critical organs. The ability to deliver an appropriate dose to a target in this area is challenging; normal organ toxicities often limit the amount of radiation that can be delivered to achieve a therapeutic dose. The modern trend in treatment of GI cancers is toward multimodality treatment. However, there is an increased risk of toxicity when combining modalities such as radiotherapy, chemotherapy, and surgery, thus placing an even greater emphasis on normal-tissue toxicities. Improvements in radiation treatment techniques over the past few decades have allowed dose escalation with improved normal-tissue sparing. The driving force behind improving treatment conformity is the significant short- and long-term morbidity of normal tissue toxicity during and after radiation treatment. The degree of normal-tissue sparing within individuals undergoing radiation treatment is highly variable and depends on tumor type and region. Tumors of the esophagus, for example, are surrounded by lung and spinal cord, while anal cancers are in close proximity to the bladder and rectum. Each subsite of the GI tract requires different techniques and approaches to maximize normal-organ sparing while delivering adequate amounts of radiation to the tumor. The physical properties of proton radiation may offer a distinct benefit in treating GI malignancies.

**Key Words:** Proton; radiation; esophageal cancer; gastric cancer; pancreatic cancer; rectal cancer; anal cancer



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## Introduction

Proton radiation therapy has gained popularity over the past few decades as a means of optimizing radiation treatment. In the field of radiation oncology there is an ever-present impetus to improve tumor killing while minimizing side effects. This is achieved by delivering higher doses of radiation to the tumor while sparing normal surrounding tissues. The most important factor in determining the success of this optimization, or therapeutic ratio, is tight control of dose conformity. However, the magnitude of normal tissue sparing in various regions of the body is variable due to specific individual anatomy. There is, in fact, evidence that patients

with high-grade acute organ toxicity during multimodality treatment seem to benefit in regard to tumor response and prognosis (1-3). This places an even greater emphasis on the need to lower radiation exposure to organs at risk. There is still a paucity of data involving the use of proton therapy in gastrointestinal malignancy due to a relative lack of clinically available proton treatment facilities worldwide.

Most of the radiation given with conventional X-ray, or photon, therapy is deposited along the entrance and exit of the beam path. In contrast, protons are small charged particles that travel only a finite distance in tissue. Most of an accelerated proton's energy is deposited as a Bragg peak

at the end of the beam path. The depth of this Bragg peak can be modulated by either varying the proton beam energy or adding compensators to the treatment gantry. Therefore, the integral dose is greatly reduced since there is no exit dose and the entrance dose is greatly reduced relative to the Bragg peak. The ability to dose-escalate at the tumor while maintaining low toxicity in normal tissues may improve the therapeutic ratio of radiation treatment. The kidneys, for example, are often involved in the radiation fields when treating gastric or pancreatic cancer. There is evidence of decline in relative renal function following kidney irradiation (4). The degree of dysfunction correlates with the amount of radiation received. These adverse outcomes emphasize the importance of sparing normal tissue from dose during radiation therapy. The use of proton therapy for treating gastrointestinal (GI) malignancy is still a topic of many ongoing studies. Nonetheless, the opportunity to improve dose distribution to highly critical organs within the abdominal cavity presents itself as a major topic of interest. We present an overview of proton therapy contributions in the role of treating esophageal, gastric, pancreatic, and rectal malignancy.

### Esophageal cancer

Esophageal cancer accounts for 5% of all GI cancers worldwide. It is the sixth leading cause of death from cancer worldwide. There is a male predominance, with the highest prevalence in Asia. The percentage and overall incidence of adenocarcinoma histology is increasing in comparison to squamous cell carcinoma histology. Tobacco, alcohol, gastroesophageal reflux (GERD), and Plummer-Vinson syndrome are known risk factors for esophageal cancer. Barrett's esophagus is an established risk factor associated with a 9-fold risk of developing adenocarcinoma of the distal esophagus (5).

Treatment options are guided by disease stage. Early stage tumors with minimal invasion have very low risk of distant metastases. They are often treated with surgical resection of the tumor. Early stage tumors with deeper invasion are generally managed with esophagectomy. Concurrent chemotherapy and radiation may be considered in patients who are not surgical candidates. Locally advanced disease is managed with up-front concurrent chemoradiation followed by re-evaluation for possible esophagectomy. Concurrent chemoradiation is considered the standard of care, yielding increased survival benefit when compared to radiation alone (6). Meta-analyses have also

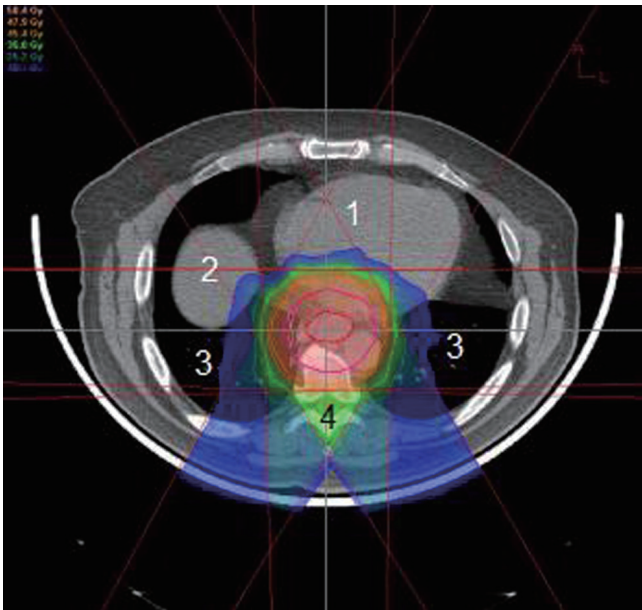
demonstrated increased survival benefit when chemoradiation is administered pre-operatively as compared to pre-operative chemo alone or no pre-operative treatment (7). Furthermore, available data suggest improvement in local control and a possible survival improvement with the use of post-operative chemoradiation as well as post-operative radiation alone (8).

The esophagus is located in the posterior mediastinum in close proximity to several critical structures, namely lung, spinal cord, and heart. Minimizing toxicities to these critical structures decreases overall treatment morbidity and mortality to the patient. However, a margin large enough to cover the areas of tumor and involved lymph nodes must be accounted for in the radiation field. This puts surrounding organs at greater risk. Lung dose is a major risk factor for toxicity during irradiation for esophageal cancer. It is often necessary to use several beams oriented at oblique angles in order to keep spinal cord dose within tolerance (*Figures 1,2,3,4*). This results in a significant amount of radiation dose received by the lung, leading to subsequent radiation pneumonitis and post-operative pulmonary complications in some patients.

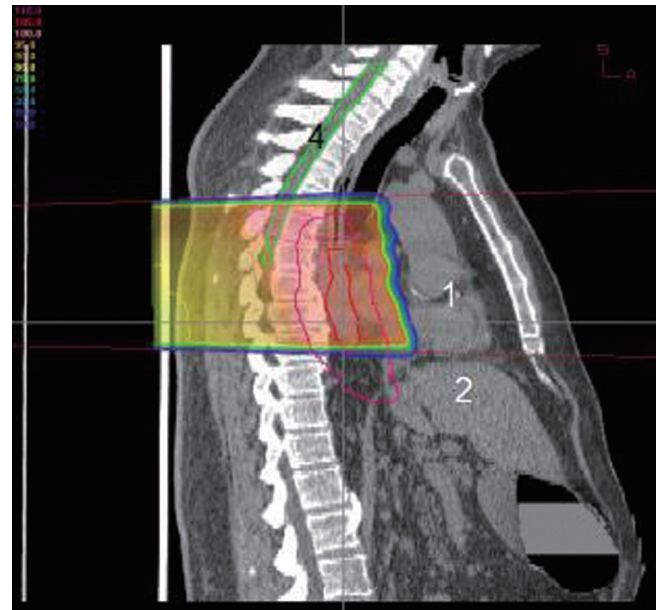
A recent phase III randomized prospective trial compared surgery alone with pre-operative concurrent chemotherapy using carboplatin and taxol given with 41.4 Gy conventional X-radiation (9). The standard radiation dose in most North American studies is 50.4 Gy, but despite the reduced dose regimen in this study the authors found improved median and overall survival in the pre-operatively treated arm compared to surgery alone. A dose of 41.4 Gy allowed the authors to use an anterior-posterior beam arrangement to spare integral dose in the lung while keeping the spinal cord dose within tolerance. The dosimetric properties of proton therapy could potentially allow safe dose escalation to 50.4 Gy or above while simultaneously sparing integral dose to the lungs and keeping the spinal cord dose within tolerance. A series of esophageal patients at M.D. Anderson Cancer Center treated with either IMRT or proton therapy found improved dose toxicity profiles when protons were used (10). While the dosimetric advantage of protons is clear, the reported clinical experience using proton beams is limited. Nonetheless several studies do report fewer interruptions during treatment due to radiation esophagitis and hematologic toxicities (11,12). The use of intensity-modulated proton beam therapy (IMPT) is the topic of several new trials in the management of esophageal cancer.

### Gastric cancer

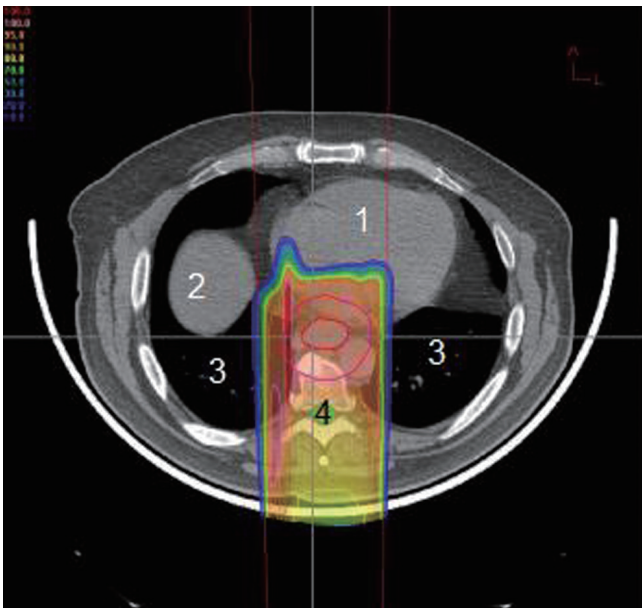
Gastric cancer has seen a sharp decrease in incidence



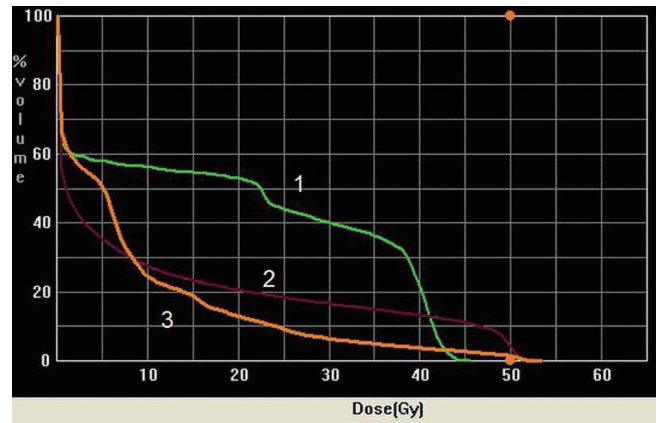
**Figure 1** Axial view of posterior oblique proton beams treating the esophagus. After reaching the esophagus the dose drops off immediately. This minimizes radiation dose received by the heart and lungs; 1. heart; 2. liver; 3. lung; 4. spinal cord



**Figure 2** Sagittal view of posterior proton beam entering the body and stopping after reaching the esophagus; 1. heart; 2. liver; 4. spinal cord



**Figure 3** Axial view of single posterior proton beam treating esophagus; Red. esophagus; Magenta. margin around the esophagus; 1. heart; 2. liver; 3. lung; 4. spinal cord



**Figure 4** Dose-volume histogram for treatment plan seen in figures 1-3 showing the amount of dose received by each organ; 1. heart; 2. liver; 3. lung

in Western countries over the past 60 years. However, the incidence of gastro-esophageal and proximal gastric tumors is increasing. It is the third most common cancer in the world and the second leading cause of cancer deaths worldwide. There is a slight male predominance, with the median age of diagnosis at 65 years. The highest death rates from gastric cancer are reported in Asia and South America. Known risk factors are smoked and salted food, pernicious anemia, and *Helicobacter Pylori* infection. Adenocarcinoma comprises the vast majority of gastric cancer histology. Positron emission tomography (PET) has achieved an increasing role in the diagnosis and staging of gastric cancers and is used as an option for greater specificity in characterizing suspected gastric tumor (13). Anatomic imaging, however, remains the standard recommendation.

Surgery has been the mainstay of treatment, although chemotherapy and radiation now have an established role. Tumors of the upper and middle third of the stomach generally require a total gastrectomy, while partial gastrectomy may be adequate for tumors located in the distal antrum. These considerations are highly variable and specific to each patient. Achieving negative margins and thorough lymph node assessment is critical in gastric cancer treatment, as the majority of recurrences are locoregional (14).

Today, the standard of care for gastric cancer is trimodality treatment or, in some institutions, perioperative chemotherapy. Surgery, chemotherapy, and radiation together all play an increasingly important role. Several landmark trials investigated the role of chemoradiation in relation to surgery. The INT0116 trial demonstrated an overall survival benefit (HR 1.32,  $P=0.0046$ ) when surgery is followed by a combination of chemoradiation (15). Gastric cancer recurrence is largely locoregional in nature. Post-operative radiation therapy is generally given to the surgical bed and surrounding lymph node regions. This results in large radiation fields that put nearby organs at risk, including lungs, liver, kidney, and small intestine. Little or no clinical prospective data exist regarding proton therapy in gastric cancer. The inherent dosimetric advantage that proton therapy provides should serve as an opportunity for improving the post-gastrectomy bed normal-organ toxicities.

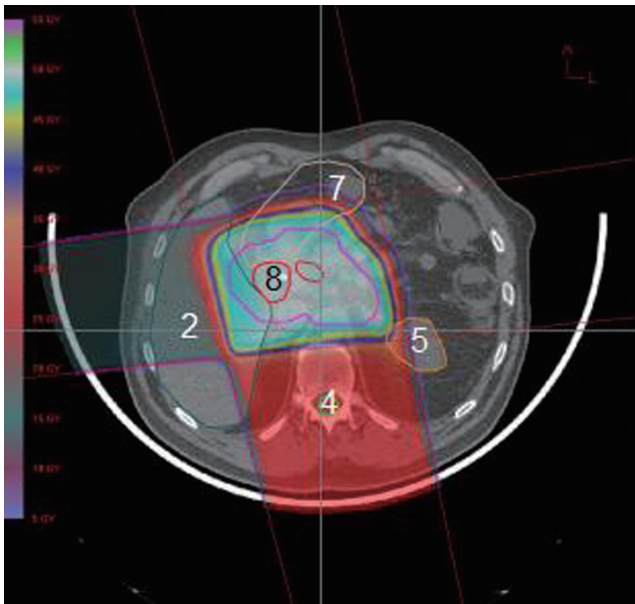
### **Pancreatic cancer**

Despite being only the tenth most common cancer worldwide, pancreatic cancer is the fourth leading cause of cancer mortality. It is found primarily in Western

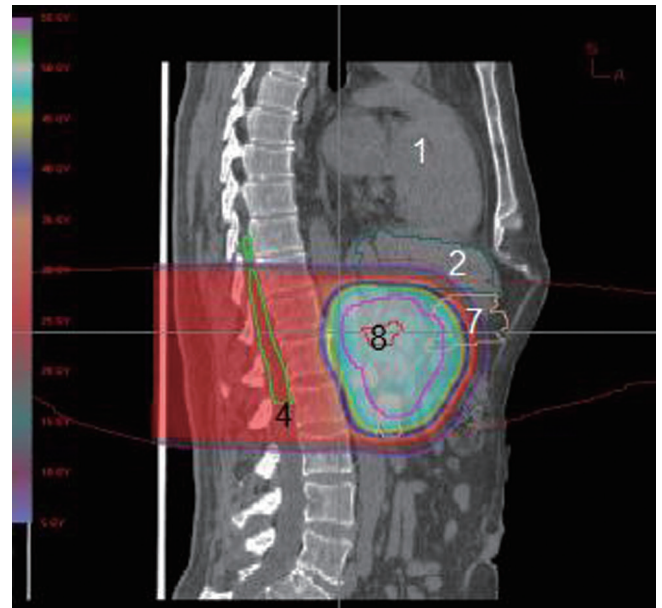
countries. Known risk factors include tobacco use, ionizing radiation, and diets high in animal fat. The incidence has been stable over the past 20 years but has increased 3-fold since 1920. It is seen more frequently in African Americans and males, with a peak incidence at 70 to 80 years of age. The most common histologic cell type is adenocarcinoma, with mucinous, serous, and neuroendocrine histologies comprising less than 10% of cases. Although elevated in some benign conditions, the tumor marker CA 19-9 is often used as a pretreatment prognostic indicator. A decreasing value after pancreatic cancer treatment is associated with better survival (16).

As a whole, pancreatic cancer carries a very poor prognosis. Nearly 80% of newly diagnosed cases are stage IV disease. Its 5-year overall survival rate is among the lowest of all cancers. Over 80% of patients who undergo surgery will have recurrence. Historically, surgery with or without chemotherapy has been the mainstay of pancreatic cancer. Chemotherapy alone has not been shown to be curative in GI malignancies. However, some promising survival data are associated with the concurrent administration of intense cytotoxic chemotherapy regimens such as fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) (17). The role of novel molecularly targeted agents is a topic of active investigation as well. When pre-operative chemotherapy or chemoradiation is administered, it is critical to assess for disease response to this treatment. Patients with disease progression during pre-operative therapy likely will not benefit from surgery and an extremely morbid surgery may be prevented (18). Patients deemed resectable typically undergo pancreaticoduodenectomy, or Whipple's Procedure, followed by chemoradiation. There is evidence for a survival benefit in giving post-operative chemoradiation over post-operative chemotherapy alone (19,20). Aside from extended survival, post-operative chemoradiation has been seen to improve performance status, reduce the amount of hospital stay, and facilitate greater pain relief (21). However, a consensus has not yet been reached defining the exact role of radiation in pancreatic cancer.

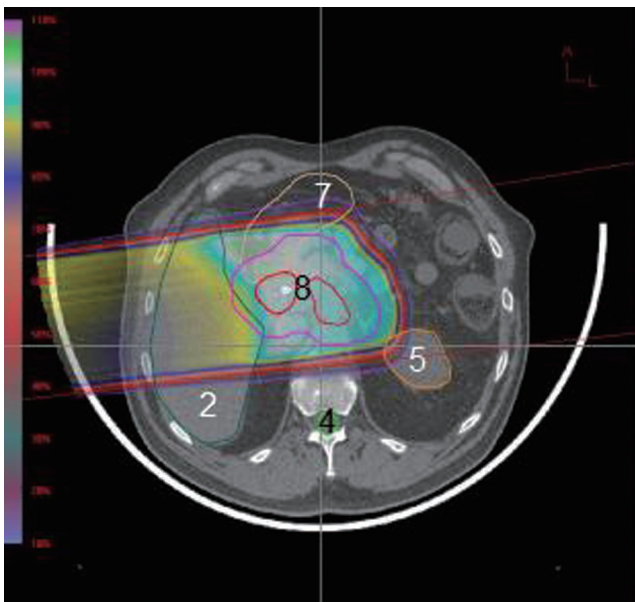
Since the value of radiation therapy in this disease has not been firmly established it is difficult to estimate the number of cases suitable for proton-beam therapy. Radiation dose escalation has shown disease control benefits for various cancer sites. Though systemic relapse is still a predominant feature, dose escalation has been shown to increase long-term disease control (22). Improvements in radiation treatment techniques, particularly in IMRT, have allowed dose escalation with acceptable normal tissue toxicities (23). Few pancreatic proton



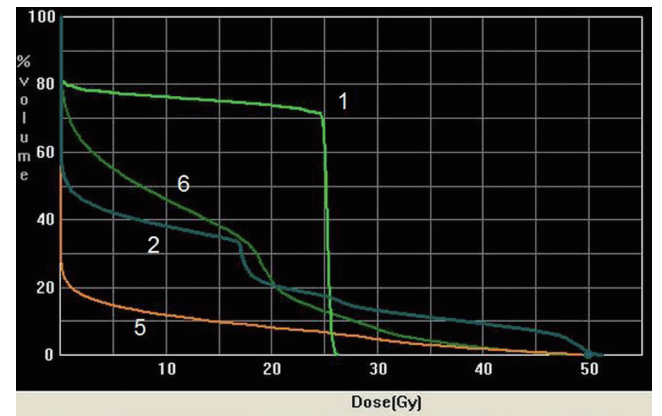
**Figure 5** Axial view of right oblique and posterior oblique proton beam entering the body to treat the postoperative pancreatic bed. The posterior beam is more heavily weighed and the dose from both beams drop off after the postoperative bed is reached; 2. liver; 4. spinal cord; 5. left kidney; 7. duodenum; 8. surgical clips



**Figure 6** Sagittal view of posterior oblique proton beam targeting postoperative pancreatic bed. This minimizes radiation dose to the liver, stomach, and bowel; 1. heart; 2. liver; 4. spinal cord; 7. duodenum; 8. surgical clips



**Figure 7** Axial view of right oblique proton beam targeting postoperative pancreatic bed; 2. liver; 4. spinal cord; 5. left kidney; 7. duodenum; 8. surgical clips



**Figure 8** Dose-volume histogram for treatment plan seen in figures 5-7 showing the amount of dose received by each organ; 1. heart; 2. liver; 5. left kidney; 6. right kidney

dosimetric data are available, but one study did demonstrate the dosimetric feasibility of five fractions of 5 Gy delivered as pre-operative pancreatic cancer treatment (24)

The pancreas is located in the retroperitoneum, closely abutting several critical organs. A proton beam's unique qualities would seem to lend itself well to such a situation (Figures 5,6,7,8). One study compared target coverage and dose-volume histograms of proton therapy plans to various 3D conformal and IMRT photon plans (25). The proton therapy plans demonstrated significantly lower integral doses. In particular, the rapid downstream falloff of dose for tumors near the ligament of Treitz enabled complete coverage of the planning target volume while staying within acceptable normal-tissue toxicity limits. In Japan concurrent proton therapy with high-dose gemcitabine has been studied, showing high feasibility and tolerability (26). The frequency of grade 3 or higher acute GI toxicities was low even when using doses as high as 70.2 GyE. Major late toxicities varied, depending on pancreatic tumor position relative to organ anatomy. Nonetheless, they were significantly reduced when using a field-in-field technique, as in this study. Proton therapy will continue to be a major focal point of investigation in future pancreatic cancer dose-escalation studies.

### Rectal cancer

The incidence of rectal cancer is equally distributed between males and females. The median age of diagnosis is the seventh decade. Associated risks factors include high-fat, low-fiber diets; animal fat; red meat; and inflammatory bowel disease. A number of gene mutations also are associated with a high risk of colon cancer. The colon and rectum are divided by the rectosigmoid junction at the level of the S3 vertebra. The rectum begins below this junction. In planning treatment for colorectal cancer one must take into account the highly variable lymph node drainage patterns, depending on the level of involvement in the colon or rectum.

The mainstay of treatment for rectal cancer remains surgery. Historically, however, surgery alone has yielded high cure rates only in early-stage rectal cancers. The addition of post-operative radiation improved local control rates but did not improve overall survival. When chemotherapy was combined with radiation, an improvement in local control, distant failures, and overall survival was seen (27). Unfortunately, many patients who undergo surgery are unable to complete chemoradiation.

Therefore, interest grew in pre-operative chemoradiation therapy. The German rectal cancer study compared pre-operative with post-operative chemoradiation and found no difference in survival rates. Pre-operative chemoradiation, however, demonstrated improved local control rates and significantly improved toxicity rates (28). Many institutions now consider pre-operative chemoradiation to be the standard of care in rectal cancer.

Isacson *et al.* initially demonstrated dosimetric advantages with proton therapy in inoperable rectal cancer patients (29). Three dose plans were made for each of six patients: one proton plan, one X-ray plan, and one mixed plan with X-ray beams followed by a proton beam boost. They demonstrated that the treatment plans involving proton beams showed superior dosimetric coverage of the target volumes. Wolff *et al.* performed a treatment planning comparison study for rectal cancer using various treatment modalities (30). Twenty-five patients with locally advanced rectal cancer were treated with pre-operative chemoradiation. The radiation was planned out using either Intensity modulated radiation therapy (IMRT), RapidArc with two arcs (full gantry rotation around the patient), 3D conformal therapy, and proton therapy. Consistently, improved systematic sparing of normal tissues as seen in the proton therapy plans while providing adequate coverage to the target regions.

Protons showed reliable and reproducible dosimetric advantages in these rectal cancer cases. The ability to spare nearby bladder, small bowel, and other normal tissue indicates an opportunity for an improved therapeutic ratio in locally advanced rectal cancers.

### Anal cancer

The past three decades has seen a marked increase in the incidence of anal cancer. Overall it is still a relatively rare malignancy, comprising less than 2% of all gastrointestinal cancers. It is seen nearly twice as often in women than in men. The mean age of diagnosis is between ages 55 and 65. Human papilloma virus (HPV) infection is strongly associated with anal squamous cell carcinoma, which comprises over 75% of cases. It is thought that HPV infection, particularly HPV-16, 18 may in fact be a requisite for disease formation. Anal cancer is associated with AIDS, although, unlike cervical cancer, it is not an AIDS-defining illness. Other risk factors include cigarette smoking, multiple sexual partners, and a history of anal warts.

Historically, abdominoperineal resection (APR) was

the standard treatment for anal cancer. This required a permanent colostomy. However, in 1973 a Wayne State study showed that pre-operative chemoradiation utilizing Fluorouracil (5-FU) and Mitomycin could induce complete pathologic responses in over 80% of patients, thus obviating the need for surgery (31). Numerous trials have established concurrent chemoradiation as superior to radiation alone (32,33). Surgical resection alone may still play a role in certain early-stage tumors with favorable characteristics. Surgery is sufficient with anal margin cancers in which the sphincter can be spared. Nonetheless, definitive chemoradiation is considered standard treatment by many institutions.

The advent of IMRT for anal cancer marked a considerable advance in treatment. Ongoing studies investigating the role of IMRT in anal cancer demonstrated promising clinical response rates with significantly better skin and normal organ toxicities as compared to conventional techniques (34). The pelvis is a tightly packed region of the body with numerous critical structures in intimate proximity to one another. Acute toxicities occur fairly frequently during treatment. Although some authorities suggest a dosimetric improvement of proton therapy over photon therapy in locally advanced anal cancer, very limited data are available for proton therapy in this disease. Traditional scanning beam techniques for proton therapy have field size limitations that make definitive proton treatment for anal cancer technically challenging. Intensity-modulated proton therapy (IMPT) techniques do not have the same field size limitations. IMPT may allow for treating anal cancer with protons with the potential of further decrease in adverse events, particularly late effects. Future studies should investigate ways to ensure adequate homogeneous coverage while sparing organs at risk.

## Conclusions

Proton therapy shows great potential to increase therapeutic tolerance for patients with gastrointestinal malignancies. Numerous studies have demonstrated the capability to reliably reproduce the dosimetric quality of conventional conformal plans. Furthermore, improved beam conformality reduces the toxicity of surrounding organs at risk. This would lead to lower rates of late toxicity. Combined modality regimens have become the standard of treatment for a great majority of GI tract cancers. Reduction in radiation toxicity to organs at risk with proton therapy may allow the use of other systemic therapy or combination

of therapies deemed too toxic when combined with conventional radiotherapy. Additionally, beam conformality with normal-tissue sparing becomes increasingly important in accordance with the general trend of finding ways to dose escalate. The possibility of decreasing radiation dose to organs at risk may also help facilitate chemotherapy dose escalation or allow for new chemotherapy combinations, which were previously deemed too toxic. The therapeutic ratio is the key parameter clinicians try to maintain in utilizing radiation therapy. Another major challenge for the future is proper identification of indications for proton therapy as a treatment modality. Proton centers are still relatively few in number; accordingly, outcomes are still fairly limited. Nonetheless, it is likely that the use of proton therapy will play a decisive role in the context of ongoing intensified combined modality treatments for GI cancers.

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