



TREATING GASTROINTESTINAL MALIGNANCY WITH PROTON THERAPY

CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES

Proton Therapy in Practice: Clinical Indications – Gastrointestinal Tumors

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FOREWORD

Since IBA first started to develop proton therapy solutions, we have focused on collaboration and sharing of information. This culture of cooperation has allowed us to work together with clinical partners to help make proton therapy available to anyone who needs it.

Our purpose is to offer more cancer patients effective treatments, decreased side effects, leading to a better quality of life.

The amount of clinical data on proton therapy is increasing rapidly, making it a challenge to keep up with new findings and advancements. We decided to take advantage of our day-to-day involvement with experienced clinical teams from proton therapy centers worldwide, in order to gather and share information on the use of proton therapy in oncology.

We've compiled this information and written a series of white papers reflecting on the latest scientific and clinical advances in proton therapy. The information that follows is the result of our in-depth review of the latest articles published in key scientific journals.

We have undertaken this information-gathering exercise with honesty and the highest level of integrity. While utmost care has been taken to ensure that the information contained in this publication is accurate, complete and unbiased, the reader should be aware that articles have been selected and data interpreted. We encourage you to interpret these data carefully and exercise your own critical and scientific judgment.

The IBA team believes in the benefits of proton therapy for patients and society. This information will help you and your teams learn more about the extraordinary promise of proton therapy, and we hope you will join us in making it accessible to more patients.

We wish you good reading,



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Gastrointestinal cancer refers to malignant conditions of the gastrointestinal (GI) tract and accessory organs of digestion, including the esophagus, stomach, biliary system, liver, pancreas, small intestine, large intestine, rectum and anus. Overall, the GI tract and the accessory organs of digestion are responsible for more cancers and more deaths from cancer than any other system in the body.^{1,2} Worldwide, hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the third leading cause of cancer-related deaths. HCC is relatively uncommon in the United States, although its incidence is rising, principally in relation to the spread of hepatitis C virus (HCV) infection.³ The incidence of pancreatic carcinoma has markedly increased over the past several decades and ranks as the fourth leading cause of cancer death in the United States. The incidence of esophageal cancer has risen in recent decades and is the eighth most common cancer globally.⁴

GASTROINTESTINAL CANCER TREATMENT

For HCC, surgical resection, liver transplantation and ablation are associated with long-term survival. The role of radiation therapy for HCC has traditionally been limited by the perceived low dose tolerance of the liver to radiation. However, recent technological developments in radiation therapy have allowed for more precise and targeted radiation therapy delivery to liver tumors. As a result of these advances, conformal liver irradiation has become feasible in the treatment of focal HCC.⁵ For pancreatic cancer, surgical resection remains the primary modality when feasible. The role of radiation remains inconclusive, but chemoradiation whether in the neoadjuvant or adjuvant setting is a standard

option often used in the U.S.⁶ Similarly, for locally advanced esophageal cancer patients, preoperative chemoradiation is associated with a survival benefit (CROSS study).⁷ For patients with esophageal cancer who are not suitable for surgery or those with squamous cell cancers, definitive chemoradiation is often employed.⁸

Radiotherapy plays a critical role in a multidisciplinary approach but the toxicity of photon-based upper-abdominal irradiation is not trivial.⁹ It is challenging because of the radiation dose tolerance of surrounding critical structures such as lung, heart and spinal cord, in the case of esophageal tumor, and stomach, bowel, liver, kidney and spinal cord in the case of liver and pancreatic cancer. Although technological advances in photon-based radiation delivery have improved in target dose conformality and the sparing of normal tissues, study data has shown that clinical outcomes are dependent on adequate dose delivered to the target, but also on the overall health of the patient, affected directly by treatment-related toxicity.

Proton therapy is different from photon-based radiotherapy owing to the unique physical property. Protons deposit the maximum dose in the tumor with much lower entrance dose and no exit dose. Proton therapy can therefore significantly reduce radiation exposure to organs at risk and healthy tissues which offers potential to reduce radiation-induced toxicities. There is a growing collection of clinical studies suggesting that proton therapy is effective for GI cancer patients, and may also improve the toxicity profile. This white paper aims to provide existing clinical data when considering treatment options that benefit patients the most.

PATIENT SELECTION

The physical properties of protons support an advantageous quality of dose distribution, offering the potential for improved therapeutic gains. The clinical interest lies in the comparative impact of proton beam therapy versus alternatives such as photon beam therapy, either as a curative solution or a salvage remedy for cancerous and noncancerous conditions and their effect on survival, disease progression, safety, health-related quality of life and other patient outcomes. An increasing emphasis on evidence-based medicine makes it worthwhile to assess the available data that supports proton therapy over other techniques to better guide the physician and patient toward the most appropriate treatment.

The current model policy developed by the American Society for Radiation Oncology (ASTRO) recommends basing patient selection on the added clinical benefit that proton therapy offers. This comes down to considering proton therapy in such cases where sparing the surrounding normal tissue is crucial and cannot be adequately achieved with a photon-based approach. The policy provides several non-specific examples:¹⁰

- The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).
- A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose 'hotspot' within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.
- A photon-based technique would increase the probability of clinically-meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity.
- The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Proton therapy may offer dosimetry advantages as well as add complexity over conventional radiotherapy. A comprehensive understanding of benefits and consequences is required by the clinicians before applying a proton technique. The decision to employ proton treatment also requires an informed assessment of benefits and risks.

PROTON THERAPY FOR GASTROINTESTINAL TUMORS

A) OVERALL BENEFITS

The improved dosimetry with proton therapy enables greater sparing of normal tissues and greater reduction in integral dose. This translates to the potential ability of escalating dose in the tumor while maintaining low toxicity, which may improve the therapeutic ratio of radiation treatment.

An increasing amount of data reported has shown that proton therapy has great potential to increase therapeutic tolerance for patients with GI malignancies. The possibility of decreasing radiation dose to organs at risk may also help facilitate chemotherapy dose escalation or allow

for new chemotherapy combinations. Proton therapy will play a decisive role in the context of ongoing intensified combined modality treatments for GI cancers.¹¹

The following review presents the benefits of proton therapy in treating hepatocellular carcinoma, pancreatic cancer and esophageal cancer.

B) DISEASE-SPECIFIC BENEFITS

• HEPATOCELLULAR CARCINOMA (HCC)

HCC is the most common primary liver cancer. Although surgical resection is the first line treatment, only around 20% of HCC patients are suitable for surgery or liver transplantation. Local ablative interventions such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) and transarterial chemoembolization (TACE) report good outcomes, but are more difficult to use for patients with larger tumors (bigger than 3-5cm), multiple lesions, lesions close to vessels and Child-Pugh B and above, due to the increasing risks of complications. Historically, radiation therapy has not played a prominent role in HCC treatment due to the concern for radiation-induced liver disease (RILD). While the recent development of photon technologies has enabled dose escalation to the tumor, one remains cautious about the acute and late toxicities.

The distinctive physical properties of proton beams confer unique advantages over photon radiotherapy. The excellent toxicity profiles and durable in-field local control rates make proton radiotherapy an attractive option for localized HCC.¹² The greater sparing of uninvolved liver using protons may be safer in patients with cirrhosis or poor liver reserve; with portal venous thrombosis that generally requires a greater volume of liver to be irradiated; and with lesions located near critical structures (see figures 1 & 2). A dosimetric study published in 2015 developed a model to predict whether protons or photons were the optimal modality for maximal liver sparing based on tumor size and location. To deliver 50Gy in 5 fractions, for patients with dome or central tumors ≥ 3 cm, proton plans significantly increased the volume of liver spared and decreased the mean liver dose, however offered no significant advantage for tumors < 3 cm at any location or for caudal and left medial tumors of any size. The authors conclude that protons should be considered as the radiation modality of choice for dome and central tumors > 3 cm as well as any tumors > 5 cm.¹³

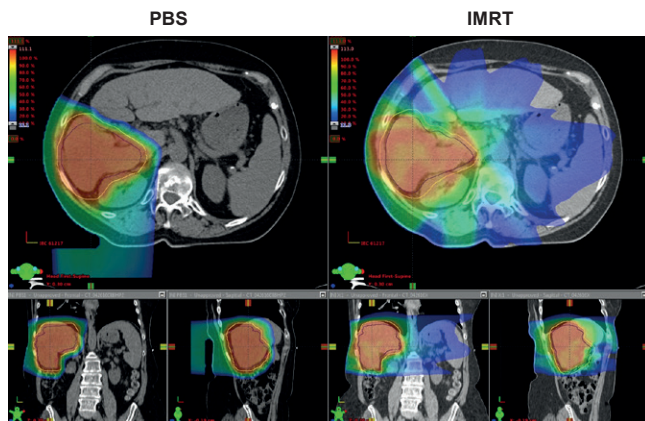


Figure 1: Radiation treatment plans comparing intensity-modulated radiation therapy 5 field (right) and pencil beam scanning proton therapy (left) for a liver tumor.

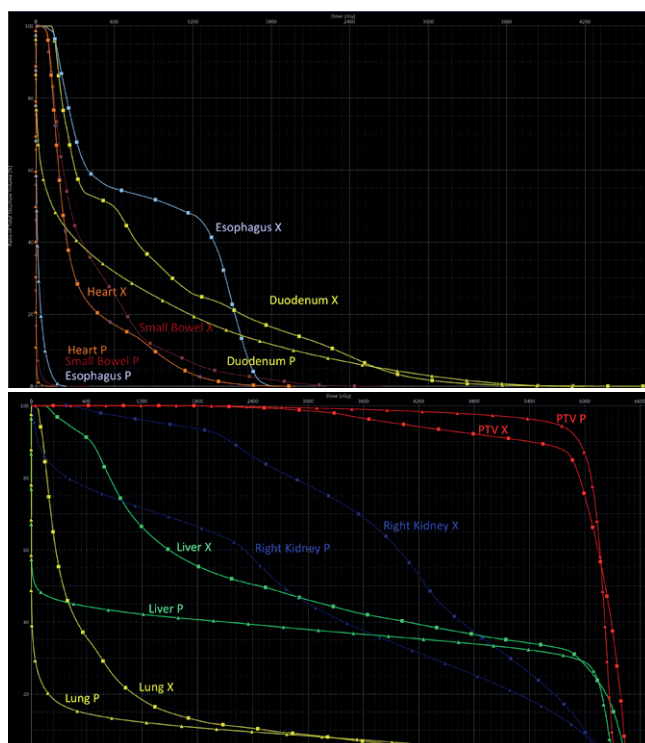


Figure 2: Dose Volume Histogram comparison between IMRT (square and labeled X) and PBS (triangle and labeled P) for PTV and organs at risk from the treatment illustrated in figure 1. All illustrations courtesy of the Department of Radiation Oncology, University of Pennsylvania.

CLINICAL OUTCOMES - LITERATURE REVIEW

Substantial experience has been published from Japan. An early study reported encouraging outcome data of 30 patients who were neither surgical nor local ablation therapy candidates with tumors between 2.5cm and 8.2cm and one-third of whom were of the Child-Pugh B type. The patients were treated with protons 76 GyE in 20 fractions. The results were a 2-year actuarial local control rate of 96% and a 2-year actuarial overall survival rate of 64%.¹⁴ Another large series followed, of 162 HCC patients treated with 72 GyE in 16

fractions. The overall survival rate for all 162 patients was 23.5% at 5 years. The local control rate at 5 years was 86.9%, and the patients had very few acute toxicities and a few late sequelae during and after the treatments.¹⁵ In a manner of higher dose hypofractionation, a cohort of 51 patients were treated with 66 GyE in 10 fractions. The overall survival rates were 49.2% and 38.7% at 3 and 5 years after treatment, with very good local control rates of 94.5% and 87.8% at 3 and 5 years after treatment. Patients experienced only minor acute toxicities of grade 1 or less, and 3 patients experienced late sequelae of grade 2 or higher.¹⁶ In treating HCC with portal vein thrombosis, 35 patients with tumor thrombi, tumor sizes ranging 2.5cm to 13cm, were treated with protons. Local progression-free survival rates were reported as 46% at 2 years and 20% at 5 years. Acute toxicity grade 3 or greater was observed in 3 patients, and no patient experienced late toxicity grade 3 or above. The authors concluded that proton therapy improved local control and significantly prolonged survival in HCC patients with portal vein tumor thrombosis (PVTT).¹⁷

In treating large HCC, a series of 22 patients with HCC larger than 10cm were treated with proton radiation; portal vein thrombosis was present in 11 patients. Tumor control rate at 2 years was 87%, and 1-year overall and progression-free survival rates were 64% and 62%, respectively. Two-year overall and progression-free survival rates were 36% and 24%. The authors concluded that proton beam therapy (PBT) represents a promising modality for the treatment of large-volume HCC.¹⁸

An analysis including 266 patients (273 HCCs) treated by PBT with 3 treatment protocols (A, 66 GyE in 10 fractions; B, 72.6 GyE in 22 fractions; and C, 77 GyE in 35 fractions), depending on the tumor location, reported overall survival rates after 1, 3 and 5 years of 87%, 61%, and 48%, respectively (median survival, 4.2 years). The local control rates after 1, 3, and 5 years were 98%, 87%, and 81%, respectively. This study showed that PBT achieved good local control for HCC using each of 3 treatment protocols and suggests that selection of treatment schedules based on tumor location may be used to reduce the risk of late toxicity and maintain good treatment efficacy.¹⁹

Similarly, a series of 343 patients who were treated with protons (242 patients) and with carbon ion therapy (101 patients) followed 8 different protocols for proton therapy and 4 different protocols for carbon ion.

Table 1: HCC literature review summary

Author	Pathology	Study	Outcome	Conclusion
Kawashima et al., 2004	HCC	retrospective analysis 30 patients proton, 76 Gy(RBE) - 20 fractions National Cancer Center Chiba	2-year actuarial control, 96% 2-year overall survival, 64% overall survival: complete resection group, 90% partial resection group, 53%	
Chiba et al., 2005	HCC	retrospective analysis 162 patients proton, 76 Gy(RBE) - 16 fractions Tsukuba University	5-year overall survival, 23.5% 5-year local control, 86.9%	very few acute reactions to treatment a few late sequelae during and after treatment
Fukumitsu et al., 2009	HCC	retrospective analysis 51 patients higher dose hypofractionation proton, 66 GyE - 10 fractions Tsukuba University	3-year overall survival, 49.2% 5-year overall survival, 38.7% 3-year local control, 94.5% 5-year local control, 87.8%	only minor acute reactions of grade 1 or less late sequelae \geq grade 2: 3 patients no treatment-related deaths
Sugahara et al., 2009	HCC with PVTT	retrospective analysis 35 patients proton Tsukuba University	2-year local progression-free survival, 46% 5-year local progression-free survival, 20% median local progression-free survival, 21 months	acute toxicity \geq grade 3: 3 patients late toxicity \geq grade 3: 0 patients proton therapy improved local control and significantly prolonged survival in HCC patients with PVTT
Sugahara et al., 2010	large HCC (>10cm)	retrospective analysis 22 patients, 11 with PVTT proton Tsukuba University	2-year tumor control, 87% 1-year local progression-free survival, 62% 1-year overall survival, 64% 2-year local progression-free survival, 24% 2-year overall survival, 36%	proton beam therapy represents a promising modality for the treatment of large-volume HCC
Mizumoto et al., 2011	HCC	comparative study 266 patients (273 HCCs) proton in 3 protocols: - 66 GyE - 10 fractions - 72.6 GyE - 22 fractions - 77 GyE - 35 fractions Tsukuba University	1-year overall survival, 87% 3-year overall survival, 61% 5-year overall survival, 48% 1-year local control, 98% 3-year local control, 87% 5-year local control, 81%	selection of treatment schedules based on tumor location may be used to reduce the risk of late toxicity and maintain good treatment efficacy
Komatsu et al., 2011	HCC	comparative study 343 patients: 242 proton, 8 different protocols 101 carbon ion, 4 different protocols Kobe University	5-year local control all patients, 90.8% 5-year local control proton patients, 90.2% 5-year local control carbon ion patients, 93% 5-year overall survival all patients, 38.2% 5-year overall survival proton patients, 38% 5-year overall survival carbon ion patients, 36.3%	proton radiation therapy, whether in combination with chemotherapy or not, results in excellent local-regional control in T4 NPC patients
Bush et al., 2014	HCC with cirrhosis	retrospective analysis 27 patients proton, median dose 55 GyE - 20 to 22 fractions National Cancer Center Korea	median progression-free survival, 36 months 3-year progression-free survival, 60%	proton therapy = safe and effective local-regional therapy for inoperable HCC
Bush et al., 2016	HCC	randomized trial 36 patients TACE 33 patients proton Loma Linda University	2-year overall survival, 59% with no difference between treatment groups	there is a trend toward improved local tumor control and progression-free survival with protons, and there are significantly fewer hospitalization days after proton treatment.

The 5-year local control and overall survival rates for all patients were 90.8% and 38.2%. The 5-year local control rates were 90.2% and 93% for proton and carbon ion therapy, respectively, and the 5-year overall survival rates were 38% and 36.3%, respectively. There was no significant difference between the two therapies. However, grade 3 and above late toxicities were observed in 8 patients on proton, 4 on carbon ion, including hematologic disorders, upper gastrointestinal ulcer, pneumonitis and subcutaneous panniculitis, as well as 4 patients who developed radiation-induced liver disease.²⁰

Similar findings have been reported from Korea. Twenty-seven HCC patients with PVTT underwent PBT. Assessments of PVTT response reported an objective response rate of 55.6%. The authors conclude that PBT could improve local progression-free survival, recurrence-free survival, and overall survival in advanced HCC patients with PVTT and that it is feasible and safe for these patients.²¹ The latest study from the same institute reported improved outcomes with dose escalation. Twenty-seven inoperable patients received PBT with 60 GyE in 20 fractions, 66 GyE in 22 fractions, or 72 GyE in 24 fractions. The complete response rates of primary tumors for dose levels 1, 2, and 3 were 62.5%, 57.1%, and 100%. The 3- and 5-year local progression-free survival rates among 26 patients were 79.9% and 63.9%, and the 3- and 5-year overall survival rates were 56.4% and 42.3%. The 3-year local progression-free survival rate was significantly higher in patients who achieved a complete response than in those who did not. The data suggests that PBT is safe and effective and an EQD2 \geq 78 GyE10 should be delivered for achievement of local tumor control.²²

In the U.S., a series of 76 HCC patients with cirrhosis reported a median progression-free survival for the entire group of 36 months, with a 60% 3-year progression-free survival rate. The authors concluded that PBT was found to be a safe and effective local-regional therapy for inoperable HCC.²³ A recent report in 2016 presented results of an interim analysis of a randomized trial comparing proton therapy with transarterial chemoembolization (TACE). Thirty-six patients received TACE and 33 received protons. The data shows similar survival rates at 2-year, and there is a trend toward improved local tumor control and progression-free survival with the proton beam treatment group.²⁴ The ASTRO model policy notes that primary HCC treated with hypofractionated regimens is within 'Group 1,' which includes other high priority groups for PBT like intraocular melanomas, chordomas and chondrosarcomas.¹⁰

DOSIMETRIC COMPARISON

Ten patients with solitary liver metastasis treated with multi-field stereotactic body radiation therapy (SBRT) were retrospectively re-planned with intensity-modulated radiation therapy (IMRT) and proton pencil beam scanning (PBS) techniques by Petersen et al. The spared liver volume for intensity-modulated proton therapy (IMPT) was higher compared to IMRT in all 10 patients. For the D(mean) \leq 15 Gy constraint, 9 of 10 cases could be treated at the highest dose level using IMPT whereas with IMRT, only 2 cases met this constraint at the highest dose level. The authors concluded that a considerable sparing of normal liver tissue can be obtained using proton-based SBRT for solitary liver tumors.²⁵

• PANCREATIC CANCER

Radiotherapy is commonly used in managing pancreatic cancer as a definitive therapy for unresectable disease and as a neoadjuvant therapy for patients with resectable tumors. However, 59% grade 3 and above non-hematologic toxicity was reported for postoperative photon-based chemoradiotherapy patients.²⁶ Proton therapy allows for significant sparing of the surrounding organs, which may be able to improve the therapeutic index and reduce toxicity caused by irradiation (see figure 3).

CLINICAL OUTCOMES - LITERATURE REVIEW

A study result published in 2012 showed that proton plans offered significantly reduced normal-tissue exposure over the IMRT plans with respect to the following: median small bowel V20 Gy, 15.4% with protons versus 47% with IMRT; median gastric V20 Gy, 2.3% with protons versus 20% with IMRT; and median right kidney V18 Gy, 27.3% with protons versus 50.5% with IMRT.²⁷ The proton radiotherapy plans were found to deliver lower mean total kidney doses, mean liver doses, and liver D1/3 compared to the IMRT plans.²⁶

The clinical toxicity outcomes support the dosimetry study. Of the 22 patients treated with proton therapy and concomitant capecitabine, no patients demonstrated any grade 3 toxicity during treatment or during the follow-up period. Some had grade 2 vomiting and diarrhea, abdominal pain, nausea and fatigue. Median weight loss during treatment was 1.3 kg (1.75% of the body weight). Chemotherapy was well-tolerated with a median 99% of the prescribed doses delivered. Proton therapy allowed a favorable toxicity profile for radiotherapy dose escalation, chemotherapy intensification, and possibly increased acceptance of preoperative radiotherapy.²⁸

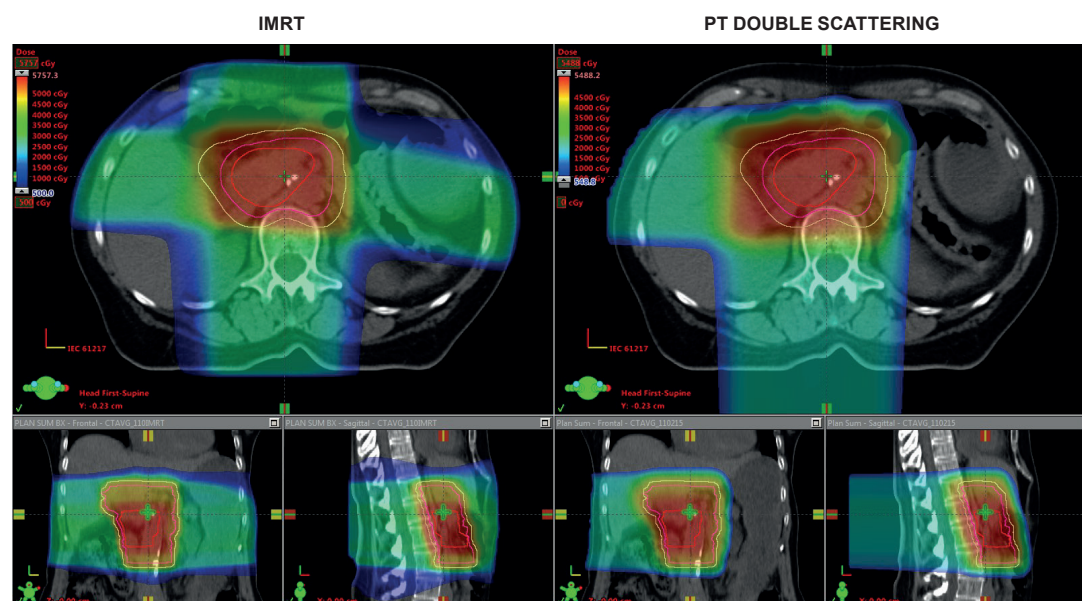


Figure 3: Radiation treatment plans comparing intensity-modulated radiation therapy 4 field (left) and proton double-scattering 2 field (right) for a post-operative pancreas tumor. Illustration courtesy of Dr. John Plastaras, Associate Professor, Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania.

Table 2: Pancreatic cancer literature review summary

Author	Pathology	Study	Outcome	Conclusion
Terashima et al., 2012	pancreatic carcinoma, locally advanced	retrospective study 50 patients proton, concurrent gemcitabine median follow-up: 12.5 months Hyogo Ion Beam Medical Center	acute hematologic or GI toxicities, 12% ≥ grade 3 late gastric ulcer and hemorrhage, 10% 1-year freedom from local progression, 81.7% 1-year progression-free survival, 64.3% 1-year overall survival, 76.8%	GPT = feasible and highly effective
Nichols et al., 2013	pancreatic and ampullary cancer	retrospective study 22 patients proton, concomitant capecitabine UFPTI	grade 3 toxicity during treatment or the follow-up period: 0 patients grade 2 gastrointestinal toxicities, 3 patients: - grade 2 vomiting: 3 patients - grade 2 diarrhea: 2 patients median 99% of prescribed chemotherapy dose delivered	proton therapy may allow for significant sparing of the small bowel and stomach associated with low rate of gastrointestinal toxicity favorable toxicity profile may allow for radiation therapy dose escalation, chemotherapy intensification, and possibly increased acceptance of preoperative radiation therapy
Takatori et al., 2014	pancreatic cancer, inoperable	prospective observational study 91 patients proton, concurrent gemcitabine Hyogo Ion Beam Medical Center	radiation-induced ulcers in stomach and duodenum, 49.4%	

In 2012, a Japanese series reported outcome data of 50 patients with locally advanced pancreatic carcinoma treated by gemcitabine-concurrent proton therapy (GPT). The scheduled GPT was feasible for all except 6 patients (12%) due to acute hematologic or GI toxicities. Grade 3 or greater late gastric ulcer and hemorrhage were seen in 5 patients (10%). The 1-year freedom from local-progression, progression-free, and overall survival rates were 81.7%, 64.3%, and 76.8%. The authors concluded that GPT was feasible and showed high efficacy.²⁹ The same group updated toxicity data of GPT in 2014, reporting that post-treatment endoscopic examinations

revealed that 45 (49.4 %) patients had radiation-induced ulcers in the stomach and duodenum.³⁰

An extensive review of articles, published in 2015, shows that the findings from dosimetric studies and early clinical outcomes suggest that proton therapy improves the therapeutic index. By reducing or eliminating the gastrointestinal toxicity associated with X-ray-based radiotherapy, proton therapy should address the concerns in postoperative setting and unresectable disease. In addition, the potential role for proton therapy is in the

neoadjuvant treatment of patients with resectable and marginally resectable disease. The researchers believe that preoperative radiotherapy would have a greater impact on securing local and regional control than chemotherapy or postoperative radiotherapy. It is possible that the favorable toxicity profile associated with proton therapy will make the preoperative radiation therapy technically feasible.³¹

DOSIMETRIC COMPARISON

Ten patients with pancreatic head adenocarcinoma treated between 2010 and 2013 were evaluated in this study. Separate treatment plans using IMRT and three-dimensional conformal radiation therapy (3DCRT) as well as proton radiotherapy were created for each patient. All planning volumes were created per RTOG 0848 protocol. Dose-volume histograms were calculated and analyzed in order to compare plans between the three modalities. The organs at risk evaluated in this study were the kidneys, liver, small bowel and spinal cord. There was no difference between the IMRT and 3DCRT plans in dose delivered to the kidneys, liver or bowel. The proton radiotherapy plans were found to deliver lower mean total kidney doses, mean liver doses and liver D1/3 compared to the IMRT plans. The proton plans also gave less mean liver dose, liver D1/3, bowel V15, and bowel V50 in comparison to the 3DCRT.^{26,32}

• ESOPHAGEAL CANCER

Radiotherapy is an important component in managing stage II and III esophageal cancers. It is administered with chemotherapy either preoperatively or definitively for non-metastatic disease. Radiotherapy is also used for palliative treatment for advanced disease. The modern radiation delivery techniques have improved dose conformity and healthy tissue sparing. A retrospective review has shown that esophageal cancer patients treated with 3DCRT had increased mortality compared to modern conformal techniques, attributed to excessive cardiovascular mortality or 'other' causes of death. Concern has been raised about the safe dose to the heart for patients undergoing a major surgery like esophagectomy, including the sub-acute and chronic phases of follow-up. IMRT can avoid the heart, but usually at the expense of lung radiation, which in turn has been associated with an increased risk of postoperative pulmonary complications correlated with mean lung dose. Protons have been compared with photons in numerous planning studies where analyses show the dosimetric advantages of protons over photons in better sparing all clinical organs such as spinal cord, lung, heart, liver and kidneys, which may result

in decreased cardiopulmonary toxicity and less morbidity to esophageal cancer patients.^{33,34,35,36} In summary, one can keep the mean heart and mean lung doses low while targeting esophageal cancers, which increasingly lie in the gastroesophageal junction, usually directly behind the heart (see figure 4).

CLINICAL OUTCOMES - LITERATURE REVIEW

Clinical outcomes for a series of 46 patients from Japan showed that the overall 5-year actuarial survival for the 23 patients with T1 tumors and for the 23 with T2 to T4 tumors were 33%, 52%, and 13%, respectively. During and after the 3 months following the radiation course grade 0 or 1 acute esophagitis was seen in 38 patients, grade 2 in 3 patients and grade 3 in 5 patients. Fifteen percent of patients developed post-irradiation ulcers within 3 months, and 63% of patients developed esophageal ulcers during subsequent follow-up. No symptomatic late complications were observed in the tracheobronchial tree, the heart or the spinal cord. The authors believe that these results appeared to be comparable to those in the best surgical series and those in the best chemoradiotherapy series.³⁷

In the U.S., a series of 62 patients, including 84% with stage II and III esophageal cancer, was treated with concurrent chemotherapy and proton therapy. The complete response rate and partial response rates were 28% and 50%. Common toxicity was reported as grade 2 to 3 acute esophagitis (46.8%), fatigue (43.6%), nausea (33.9%), anorexia (30.1%), and radiation dermatitis (16.1%). The conclusion was that the proton modality is associated with few severe toxicities and the pathologic response and clinical outcomes are encouraging.³⁸ A multi-institutional retrospective analysis in 2015 examined the impact of neoadjuvant proton versus photon chemoradiotherapy on postoperative outcomes in esophageal cancer patients. The report showed that proton therapy patients had less acute grade 2 nausea (28.8% versus 50.3%, $p=0.001$), fatigue (27% versus 33.1%, $p=0.001$), and hematologic toxicity (1.8% versus 25.5%, $p=0.001$) compared to photon therapy groups.³⁹ The conclusion of the analysis was that neoadjuvant proton radiotherapy was associated with a lower rate of postoperative complications and a shorter length of stay at the hospital, compared to photon radiotherapy. Overall survival was superior with proton versus photon radiotherapy, although this difference was not statistically significant.⁴⁰ A recent report from 2016 shows positive data supporting proton reirradiation for recurrent esophageal cancer.⁴¹

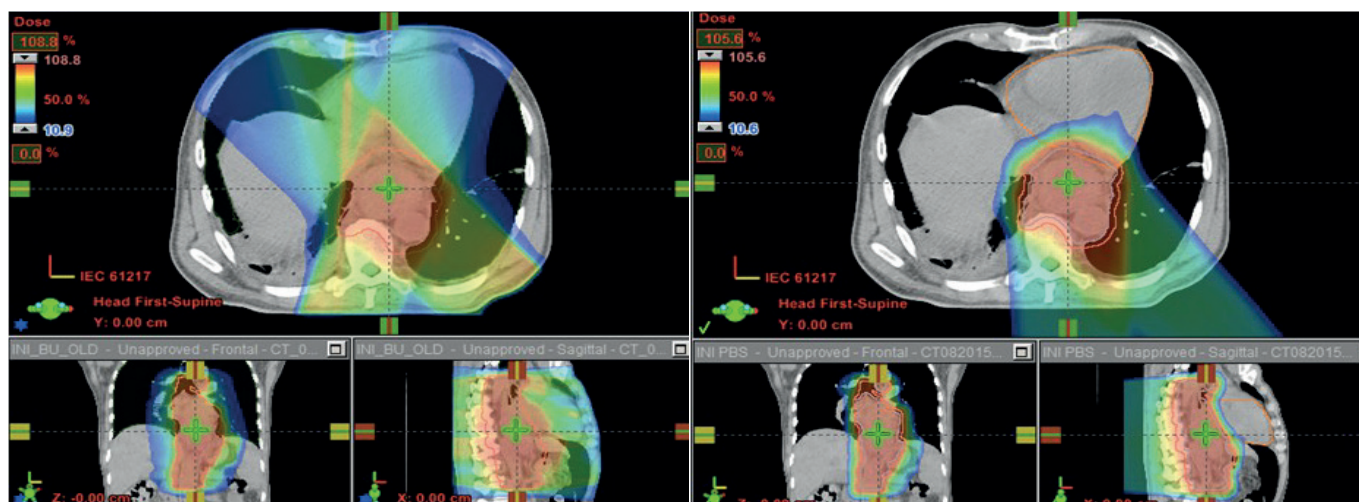


Figure 4: Radiation treatment plans comparing intensity-modulated radiation therapy (top) and proton therapy (bottom) for an esophageal cancer. Illustration courtesy of Dr. John Plastaras, Associate Professor, Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania.

Table 3: Esophageal cancer literature review summary

Author	Pathology	Study	Outcome	Conclusion
Tokuuye et al., 2008	esophageal cancer	retrospective study 46 patients: - 23 T1 tumors - 23 T2-T4 tumors Tsukuba University	5-year overall survival, 33%: - 23 T1, 52% - 23 T2-T4, 13% acute esophagitis up till 3 months after radiation: - grade 0-1, 38 patients - grade 2, 3 patients - grade 3, 5 patients post-irradiation ulcers: - 15% within 3 months - 63% esophageal ulcer during subsequent follow-up	no symptomatic late complications observed in tracheobronchial tree, heart, spinal cord results comparable to those in best surgical series and those in best chemoradiotherapy series
Lin et al., 2012	esophageal cancer	retrospective study 62 patients, 84% stage II and III proton, concurrent chemotherapy Tsukuba University	complete response, 28% partial response, 50% grade 2 to 3 acute: - esophagitis, 46.8% - fatigue, 43.6% - nausea, 33.9% - anorexia, 30.1% - radiation dermatitis, 16.1%	proton associated with a few severe toxicities pathologic response and clinical outcomes are encouraging
Ling et al., 2014	esophageal cancer	comparative study 10 patients proton, IMRT, 3DCRT Loma Linda University	proton plans showed decreased dose to various volumes of heart & lungs ↔ IMRT & 3DCRT plans	proton plans: technically feasible while achieving adequate coverage with lower doses delivered to the lungs and cardiac structures this may result in decreased cardiopulmonary toxicity and less morbidity

DOSIMETRIC COMPARISON

Various articles compare the dosimetric advantage of radiotherapy compared to passive beam scattering or IMPT. A recent review of these articles by Chuong concluded that further risk reductions are achieved with proton therapy.

Although IMRT provides good dose conformity and reduces dose radiation exposure to normal tissues compared to

3DCRT, the use of PBS proton therapy further decreases the dose to surrounding organs at risk while providing similar conformity. This may result in decreasing cardiac toxicity and pulmonary complications that are the two major causes of morbidity in esophageal cancer patients.

C) REFERENCE TO ONGOING STUDIES

• LIVER CANCER

There are nine studies registered on the ClinicalTrials.gov registry and results database investigating proton therapy for liver cancer, including eight on HCC and one about liver metastasis. In addition to phase II studies looking into efficacy and toxicity, there are four randomized comparison trials.

The Loma Linda University in the U.S. leads two randomized comparison trials. The randomized controlled trial of transarterial chemoembolization versus proton beam radiotherapy for the treatment of hepatocellular carcinoma will enroll 200 patients. The outcome measures

are overall survival, time to progression and downstaging. Another randomized control trial compares proton radiotherapy plus sorafenib versus sorafenib alone for patients with hepatocellular carcinoma exceeding San Francisco Criteria. Two hundred and twenty patients are to be enrolled. The outcome measures are set as overall survival and radiological progression.

Korea National Cancer Center leads another randomized comparison study looking into radiofrequency ablation versus hypofractionated proton radiation for patients with recurrent/residual small hepatocellular carcinoma. The study enrolled 144 patients with HCC who had a recurrent or residual tumor after other treatments but without pre-irradiation. The inclusion criteria specify that the largest diameter of the

Table 4: HCC ongoing studies

Title	Site	Type	Randomized	Comparative	PI	Endpoint
Proton Radiotherapy Versus Radiofrequency Ablation for Patients With Medium or Large Hepatocellular Carcinoma	HCC	phase III	yes	yes	Chang Gung Memorial, Taiwan	survival rates
Proton Beam Irradiation for the Treatment of Unresectable Hepatocellular Cancer and Cholangiocarcinoma	HCC	phase II			MGH, US	2-year LC, 5-year OS
Transarterial Chemoembolization Versus Proton Beam Radiotherapy for the Treatment of Hepatocellular Carcinoma	HCC	phase III	yes	yes	Loma Linda University, US	OS, time to progression, downstaging
Proton Beam Radiotherapy Plus Sorafenib Versus Sorafenib for Patients With Hepatocellular Carcinoma Exceeding San Francisco Criteria	HCC	phase II	yes	yes	Loma Linda University, US	OS
Hypofractionated Proton Beam Radiotherapy for Inoperable Hepatocellular Carcinoma	HCC hypofrac	phase II			NCC Korea	LPFS, OS
Hypofractionated Proton Beam Radiotherapy for Hepatocellular Carcinoma	HCC hypofrac	phase II			NCC Korea	LPFS, OS
Proton Therapy in the Treatment of Liver Metastases	liver mets	phase I			Loma Linda University, US	safety, tolerability, LC
Feasibility of High Dose Proton Therapy On Unresectable Primary Carcinoma Of Liver: Prospective Phase II Trial	HCC	phase II			Samsung Medical Center, Korea	OS, LC, toxicity
Proton Beam Therapy in Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis	HCC	phase II			Samsung Medical Center, Korea	OS, LC, toxicity
Comparison Between Radiofrequency Ablation and Hypofractionated Proton Beam Radiation for Recurrent/Residual HCC	HCC	phase III	yes	yes	NCC Korea	LPFS, DFS, OS at 2-year

tumor should be less than 3cm, and the number of tumors ≤ 2 . Proton therapy is administered in 66 GyE /10 fx, 6.6 GyE fraction dose, 5 days/week. The study measures local progression-free survival, disease free survival and overall survival at 2 years.

Chang Gung Memorial Hospital in Taiwan leads a trial looking into medium or large tumors treated with RFA and proton therapy. The trial tests PBT versus switching control radiofrequency ablation for patients with medium (>3 , ≤ 5 cm) or large (>5 , ≤ 7 cm) treatment-naïve hepatocellular carcinoma, and is scheduled to enroll 166 patients. The primary endpoint is the local control rate at 3-year and secondary measures include local control, distant metastasis free survival, overall survival and patient report outcomes.

• PANCREATIC CANCER

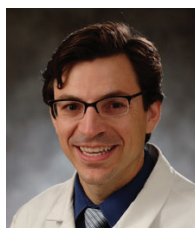
There are eight trials registered with ClinicalTrials.gov investigating proton therapy combined with chemotherapy in treating pancreatic cancer.

University of Florida leads three studies looking into protons plus chemotherapy for resectable, unresectable and postoperative pancreatic cancer. Massachusetts General Hospital (MGH) has three efficacy studies looking into proton therapy combined with different chemo-agents. A University of Pennsylvania study is investigating dose escalation in both a novel chemo therapy agent and radiation dose for locally advanced pancreatic cancer.

Table 5: Pancreatic cancer ongoing studies

Title	Type	PI	Endpoint
Postoperative Proton Radiotherapy With Chemo for Pancreatic Cancer	phase II	University of Florida, US	radiation toxicity, local control
Proton Radiation for Unresectable, Borderline Resectable, or Medically Inoperable Carcinoma of the Pancreas (PC04)	phase II	University of Florida, US	efficacy/safety
Proton Radiation for Resectable Carcinoma of the Pancreas	phase II	University of Florida, US	toxicity, tumor control
Proton w/FOLFIRINOX-Losartan for Pancreatic Cancer	phase II	MGH, US	feasibility, PFS, toxicity
Short Course Radiation Therapy With Proton or Photon Beam Capecitabine and Hydroxychloroquine for Resectable Pancreatic Cancer	phase II	MGH, US	LPFS, response rate, OS, toxicity
Chemotherapy Plus Proton-chemotherapy for Locally Advanced Pancreatic Cancer	phase II	Loma Linda University, US	1-year OS, toxicity
FOLFIRINOX + RT for Pancreatic Cancer	phase II	MGH, US	rate of resection, PFS
A Phase I Dual Dose Escalation Study of Radiation and Nab-Paclitaxel in Patients With Unresectable and Borderline Resectable Pancreatic Cancer	phase I	Upenn, US	efficacy and toxicity
Proton Beam Therapy in Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis	HCC	phase II	
Comparison Between Radiofrequency Ablation and Hypofractionated Proton Beam Radiation for Recurrent/Residual HCC	HCC	phase III	yes

D) THE EXPERT'S PERSPECTIVE



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• THE PRESENT

When asked about his current experiences with proton therapy, Dr. Plastaras points out that proton therapy is currently being used as a routine standard of care in many GI cancers in regions where proton therapy is accessible. "In particular, liver tumors, pancreas, and esophagus cancers are common disease sites where practitioners are especially concerned by the toxicity of radiation and will use whatever tools exist to allow treatment without excessive side effects. However proton therapy is also used for other GI sites in select cases, such as ano-rectal cancers, cholangiocarcinomas, duodenal cancers, and gastric cancer," he says. "HCC is listed in 'Group 1' in the ASTRO model policy on proton therapy, indicating the widest acceptance of use based on existing data. Reirradiation

is also listed in Group 1, and this is another area where proton therapy for recurrent GI cancers is used routinely in very well-selected patients. 'Thoracic' malignancies, which would include esophageal cancer and 'Abdominal' or 'Pelvic' malignancies, which would include pancreas and other GI cancers are all listed in 'Group 2,' which indicates a 'need for continued clinical evidence development.' ASTRO suggests that these sites be covered by insurance companies when patients are enrolled in clinical trials or registries."

Dr. Plastaras explains how, in general, radiotherapy is being omitted as frequently as possible in multidisciplinary clinics due to toxicity concerns, especially when a survival benefit cannot be proven. If the target can be treated robustly and reliably, then most GI radiation oncologists welcome any technique to avoid any additional radiation to sensitive structures. "These decisions are made individually for each patient and the potential for proton therapy to be preferred depends on the anatomy, motion, and available technologies."

• THE FUTURE

The future of proton therapy in GI cancers will evolve on several fronts, according to Dr. Plastaras. "The first is further refining the technical aspects of treating a variety of GI cancer sites with emerging tools like breath hold and gating paired with PBS and IMPT. Robustness optimization during the planning process will be important when targeting GI sites with variable bowel gas and motion. Incorporating onboard 3-dimensional imaging during proton therapy will further enhance our understanding of how the conformality envelope can be pushed, similar to how CBCT (cone beam CT) allowed the widespread adoption of linac-based SBRT (stereotactic body radiation therapy). The second important development will be quantifying the clinical toxicity benefit that can be achieved with proton therapy. A variety of phase II studies are underway that will help characterize the observed toxicity rates when proton therapy is delivered with either standard chemotherapy or novel sensitizing agents. Once complete, comparative effectiveness studies can be appropriately powered to measure the differences between photon and proton-based chemoradiation with those concurrent systemic agents. A third area of development will be exploring how dose escalation, presumably only achievable with proton therapy, can improve efficacy outcomes compared to existing standards of care."

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