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15.1 Introduction

15.1.1 Pancreatic Cancer

- Pancreatic cancer is a morbid disease with a high mortality rate, and patients are often diagnosed with metastatic disease at presentation. Approximately 53,000 patients were diagnosed with pancreatic cancer in 2016, and only 7.7% of them will be alive in 5 years [1, 2]. Despite the high rate of distant dissemination, up to 30% of patients die of local disease progression [3]. While the treatment paradigm for

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pancreatic cancer may change with the development of prognostic and predictive biomarkers to help determine who may benefit from local treatment versus systemic treatment, we currently utilize surgical resection when patients have resectable disease followed by adjuvant chemotherapy, with or without adjuvant chemoradiation. Patients with borderline or unresectable disease are treated with chemotherapy, and we often utilize chemoradiation for local disease control with some patients who had borderline resectable disease subsequently able to undergo surgical resection.

- Local failure occurs in about 50 percent of patients following resection and results in considerable morbidity and mortality. The use of postoperative radiation is supported by the GITSG 91-73 study, which showed an increased median survival from 11 to 20 months with chemoradiation following surgery compared to observation alone [4]. RTOG 9704 also reported on adjuvant chemoradiation, with a median survival of 20.5 months in the concurrent gemcitabine and radiation arm [5]. However, the use of adjuvant radiation has been controversial, since the CONKO-001 study of chemotherapy versus observation showed gemcitabine alone conferred a median survival of 22.8 months [6], EORTC 40891 showed no difference between chemoradiation and observation [7], and ESPAC-1 showed a benefit to chemotherapy over chemoradiation [8]. It is important to note that in the EORTC study, 45% of patients had ampullary cancer (with a better prognosis), so it was likely underpowered to detect a survival advantage in the pancreatic cancer patients, and 20% of the chemoradiation arm did not receive the prescribed regimen. There is also very strong evidence for adjuvant chemoradiation in large retrospective case series from Johns Hopkins and the Mayo Clinic showing the median survival extended from 11 to 20 months with adjuvant chemoradiation [9]. A National Cancer Database study using propensity score analysis in 11,526 patients revealed that chemoradiation was associated with improved overall survival, compared to adjuvant chemotherapy alone, when each was matched to surgery alone with a hazard ratio of 0.7–1.04, respectively [10]. The phase III RTOG 0848 trial of resected pancreatic head tumors treated with five cycles of adjuvant gemcitabine ± erlotinib and then, if free from progression, randomized to an additional cycle of chemotherapy or an additional cycle followed by chemoradiation is currently open to accrual and will help determine the optimal adjuvant regimen.
- There is evidence that for borderline resectable disease, local radiation treatment with concurrent high-dose chemotherapy offers a survival advantage, improved disease control, and the potential for a high rate of an R0 resection. A multi-institutional phase II trial of systemic dosing gemcitabine and oxaliplatin with radiation (30 Gy in 15 fractions) resulted in a 63% resection rate, 84% of which had negative margins, and a median survival of 18 months [11]. The benefit of chemoradiation compared to chemotherapy alone in unresectable disease has been controversial. The limitations in the intact setting have been toxicity to the upper abdominal structures as a result of the large radiation fields needed to cover the gross tumor volume in the 3D conformal era. The ECOG 4201 randomized phase II study of gemcitabine alone versus gemcitabine with concurrent conventional radiation (IMRT not allowed) showed an improved median survival and decreased local recurrence with radiation but with substantial grade 3 and 4 toxicities [12]. A phase I/II study from the University of Michigan evaluated high-dose conformal IMRT with concurrent gemcitabine and showed an

increased median survival of 14.8 months and an increased freedom from local progression of 60% compared to historical controls [13]. More recently, the Lap 07 trial randomized unresectable patients to gemcitabine versus gemcitabine + erlotinib, and then patients without progression were additionally randomized to chemoradiation, 54 Gy with concurrent capecitabine, versus additional chemotherapy [14]. The results showed no significant difference in overall survival between chemoradiation and chemotherapy alone but did show decreased locoregional progression in patients receiving chemoradiation. There are many patients for whom local progression results in significant morbidity and mortality. Autopsy series have reported that up to 30 percent of patients die of local disease progression which was correlated with the expression of SMAD4, indicating there are patients for whom local disease control is very important [3]. Local progression of unresected pancreatic cancer can also result in significant morbidity with obstructive symptoms, bleeding, bowel perforation, and pain necessitating palliation even in the patient with metastatic disease.

- With little improvement in survival seen in studies of chemoradiation using modest radiation doses (~50–54 Gy in 1.8–2 Gy fractions), dose escalation has been attempted with 3D conformal radiation, resulting in significant gastrointestinal toxicities [15]. Studies utilizing IMRT have reported lower rates of acute grade 3 nausea and vomiting, diarrhea, and late gastrointestinal toxicities such as duodenal ulceration compared to studies using 3D conformal radiation [16]. However, IMRT dose escalation with concurrent gemcitabine also resulted in significant toxicities, with 24% of patients experiencing grade 3 or 4 dose-limiting toxicities [13]. SBRT has been evaluated for unresectable disease with comparable median survival to conventional fractionation and with increased concern for acute gastrointestinal toxicity when the disease is in close proximity to or invading the duodenum [17]. In theory, proton radiation with its characteristic Bragg peak and rapid falloff at the distal end of the proton beam could be superior to IMRT or SBRT in sparing normal tissues. In practice, however, range uncertainties related to CT calibration, organ motion, and patient setup have necessitated an increase in margins in proton therapy. As double-scattered (DS) and uniform scanning (US) proton therapy cannot modify beam portal along their beam path, conformality is increased with pencil beam scanning (PBS) compared to DS and US.

15.1.2 Gastric Cancer

- While the incidence of gastric cancer is declining, it still contributes significantly to cancer mortality as the third leading cause of cancer-related death worldwide. In locally advanced and node-positive disease, surgery with lymphadenectomy is the mainstay of treatment. The use of perioperative chemotherapy and/or adjuvant chemoradiation has been controversial. Neoadjuvant and adjuvant chemotherapy may be offered based on results of the MAGIC trial of perioperative chemotherapy showing increased overall survival and improved progression-free survival compared to surgery alone. Alternatively, patients may proceed with

surgery and then receive adjuvant chemoradiation, done frequently in the United States, based on results of the North American Intergroup 0116 trial showing a survival advantage. Practically, the decision to offer perioperative chemotherapy or adjuvant chemoradiation may depend on the local extent of disease, resectability at presentation, and pathologic risk factors after resection such as the margin status and extent of the lymph node dissection.

- The surgical approach for stomach tumors is either a total gastrectomy for proximal 1/3 and diffuse gastric malignancies or a subtotal gastrectomy for tumors of the gastric antrum (distal 2/3) [18]. Surgical margins are very important due to the infiltrative nature, and a 5 cm proximal and distal margin has historically been recommended. However, recent multi-institutional retrospective analysis of distal gastric cancers indicated that 3 cm may be adequate [19]. There are 16 lymph node stations, and the extent of their dissection is described in the surgical literature. A D1 lymph node dissection is the removal of the adjacent perigastric lymph nodes (stations 1–6) alone; a D2 dissection includes the additional dissection of the hepatic, left gastric, celiac, and splenic nodes (stations 1–11) as well as a splenectomy; and a D3 dissection additionally adds the porta hepatic and periaortic nodes (stations 1–16). In practice a D2 dissection with removal of at least 15 lymph nodes is recommended, but this is often dependent on the experience of the surgeon performing the surgery, and many patients have much more limited D1 dissections with fewer lymph nodes removed.
- Adjuvant chemoradiation is often offered based on the results of the Intergroup 0166 randomized trial of postoperative radiation with 45 Gy and fluorouracil and leucovorin versus observation. The 3-year overall survival was significantly increased to 50% in patients receiving chemoradiation from 41% with observation alone, supporting the use of adjuvant chemoradiation [20]. In this trial a D2 lymph node dissection was recommended; however, only 9.6% had a D2, 36% had a D1, and 54% had less than a D1 lymph node dissection. These results imply that chemoradiation may benefit a population without an adequate lymphadenectomy. The acute toxicity rate was also significant in this study in the 2D planning era, with 54% hematologic and 33% gastrointestinal grade 3 or greater toxicity. Seventeen percent stopped treatment due to toxicity and there was a 1% death rate. The ARTIST I trial evaluated adjuvant chemotherapy versus chemoradiation in patients who underwent a D2 lymph node dissection and found no survival or distant metastasis-free survival difference [21]. However, there was a significant decrease in local relapse rate with chemoradiation which can cause significant morbidity in this population. A subset analysis of the ARTIST I trial found a disease-free survival benefit in patients with lymph node-positive disease, and the ARTIST II trial is currently evaluating the benefit of chemoradiation in lymph node-positive disease. It is also important to note that on subset analysis of the INT-0116 trial, there appeared to be a reduced effect of chemoradiation in patients with diffuse-type histology. The ARTIST I trial had a high proportion of patients with diffuse-type histology (63% in the chemoradiation arm) which we know have worse outcomes and may have made it difficult to show a benefit.

- There are patients who benefit from adjuvant chemoradiation, and likely those with positive lymph nodes, less than a D2 lymph node dissection, and positive or inadequate surgical margins benefit more from adjuvant radiation treatment. The treatment volume encompasses the tumor bed, the remaining stomach, anastomoses, hepatogastric ligament, and at-risk and dissected lymph node volumes. With a large treatment volume, it is important that we utilize advances in radiation treatment delivery with more conformal techniques to reduce toxicity. Three-dimensional conformal treatment has been compared with IMRT and was found to increase conformality and decrease the dose to the spinal cord, kidneys, liver, and heart [22]. Proton beam radiation is promising as another treatment modality in gastric malignancy to spare dose to nearby OARs with the potential to decrease toxicity.

15.2 Simulation and Motion Management

Robust indexed immobilization is strongly recommended when treating pancreatic and gastric malignancies to minimize interfraction patient setup error. Immobilization vacuum bags can be used provided that the bag volume does not change through the course of treatment, as variation in bag volume can perturb the proton beam range. If used, bag volume should be verified with imaging prior to each treatment. Alternatively, simulation and treatment may be performed using a wing board or alpha cradle and indexed knee lock to prevent rotation in the legs and hips (Fig. 15.1). Simulation scans should be performed in the supine position with arms up and away from the treatment area. Scans should be acquired from the carina to below the iliac crest.

Non-contrast CT scans should be obtained for treatment planning for the purpose of dose calculation. A high-resolution CT scan (slice thickness of 3 mm or less) with IV contrast may be subsequently performed for improved delineation of the primary tumor, vasculature, and lymph nodes. Volumen (0.1% barium suspension),

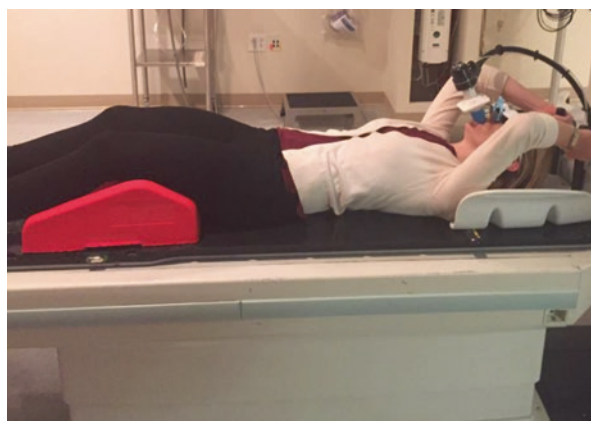


Fig. 15.1 Simulation is done supine using indexed wing board and knee lock. Note: for actual treatment, patient should have minimal clothing on to avoid perturbation of proton beam



Fig. 15.2 (a) Volumetric oral contrast, when used with IV contrast, allows for improved mural detail in the duodenum and bowel. (b) Barium as an oral contrast agent

a negative oral contrast agent with low attenuation (Fig. 15.2a), allows for excellent distention as well as superior visualization of mural detail of the duodenum and small intestine with CT imaging [23]. It is recommended that contrast scans be performed subsequent to scans used for treatment planning; however, if that is not possible, any material existing in the planning scan which will not be present for treatment must be overridden and assigned appropriate Hounsfield unit (HU) values. Of note, metal mesh stents in the common bile duct do not perturb the proton dose distribution and do not need to be overridden. Additional imaging such as diagnostic-quality CT, PET-CT, and/or MRI may also be useful to visualize involved lymph nodes, extent of gross disease, and recurrent disease. In the case of postoperative radiation, preoperative imaging should also be used when delineating the target volume. If possible, all scans should be acquired with the patient in the same position as CT simulation for improved accuracy in image registration. Patients are instructed to not take anything by mouth (NPO) for a minimum of 3 hours prior to simulation to decrease variability in gastric volume. Patients may be given specific dietary instructions to be NPO for a few hours prior to treatment fractions as well, depending on the location of the target and its proximity to the stomach or when treating gastric cancer. For example, when treating gastric adenocarcinoma after a subtotal gastrectomy at our institution, patients are instructed to withhold food and fluid consumption for 3 hours prior to simulation and daily treatment so that stomach and bowel volumes are reproducible.

Respiratory- and gastrointestinal-induced motion management is an important component of treating thoracic and abdominal malignancies as these regions routinely exhibit significant motion [24, 25]. An in-depth analysis of motion mitigation techniques is beyond the scope of this chapter, although Task Group 76 of the American Association of Physicists in Medicine discusses a comprehensive overview of available options [26]. Several motion mitigation methods are employed at our institution when treating pancreatic and gastric targets, depending on the degree of anatomical motion exhibited by the patient. These methods include using respiratory-correlated (or 4DCT) scans and adding an ITV to account for motion,

deep inspiration breath hold (DIBH), or abdominal compression. The modality of motion management is particularly important for unresected pancreatic adenocarcinoma, since the tumor and duodenum are usually in close proximity. We recommend motion management with breath hold (involuntary with Active Breathing Control, ABC, or voluntary deep inspiratory breath hold, DIBH, with SDX), when treating unresected pancreatic tumors.

Fluoroscopy can be useful in identifying the degree of a patient's anatomical motion [27–30]. At our institution, patients who are being simulated for an abdominal malignancy may undergo a pre-simulation fluoroscopy session to assess the degree of motion and determine which method may be the best option to mitigate or account for motion during treatment (Fig. 15.3). Not all abdominal lesions can be clearly visualized on fluoroscopy and should be administered on a per-patient basis. Visualization techniques may aid in delineating volumes of interest in the fluoroscopy, such as implanted markers, oral contrast to distinguish stomach volume, or nearby visible landmarks whose motion may act as a surrogate for the region of interest (for example, the liver or diaphragm). In general, patients with less than 5 mm of motion undergo 4DCT scans, with treatment planning being performed on the CT scan comprised of the average of all breathing phases. Patients with greater than 5 mm of motion may require DIBH or abdominal compression to reduce the

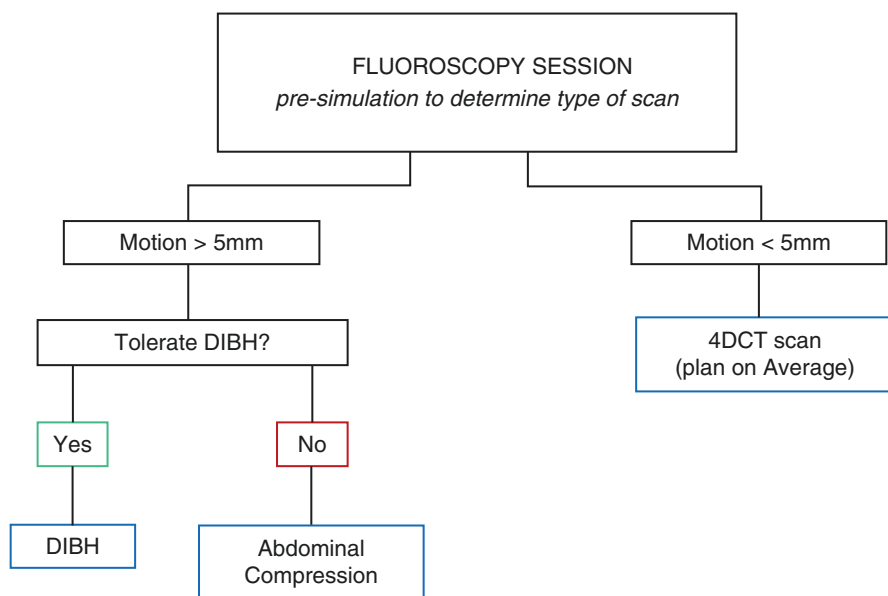


Fig. 15.3 Example of workflow diagram from pre-simulation fluoroscopy session to determine type of motion management used. General practice at our institution is that if motion is less than 5 mm, planning is performed on a free-breathing average CT scan. If motion is greater than 5 mm and DIBH is tolerated, SDX or ABC device is utilized for DIBH. If not tolerated, abdominal compression using a belt is utilized. Motion should be carefully evaluated by the treating team on a per patient basis

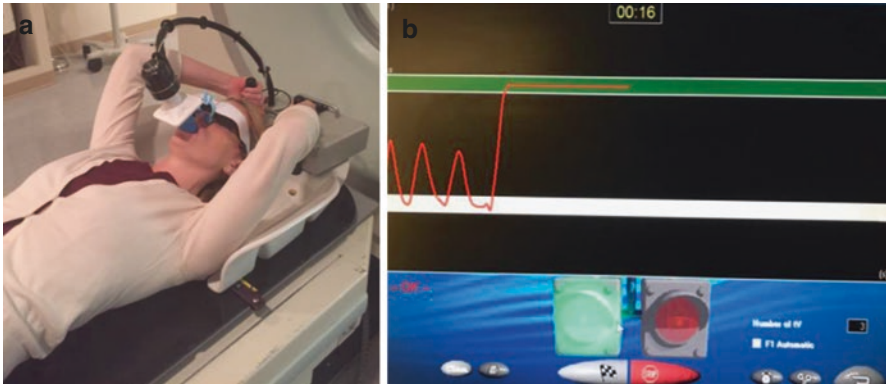


Fig. 15.4 (a) Voluntary DIBH using spirometric motion management is shown. (b) Patient interface when using voluntary breath-hold SDX system. Therapists are instructed to turn the treatment beam on during the predefined inhale region (shown in *green*)

amount of anatomical motion. DIBH may be achieved using a device such as the Active Breathing Control or ABC (Elekta Medical Systems, Stockholm, Sweden) or the Spirometric Motion Management System or SDX (Qfix, Avondale, PA), both of which have been implemented at our institution (Fig. 15.4). Because SDX requires patient compliance and the ability to hold one's breath as instructed, abdominal compression using a compression belt may be more tolerable. One advantage of the ABC device over SDX is that with ABC the time of breath hold is controlled by the therapist (rather than by the patients). This allows for correct timing of the administration of IV contrast. Contrast-enhanced scans using breath hold with the SDX device are very difficult to obtain.

An important consideration when using abdominal compression is minimizing variability in anatomical deformation caused by the belt. It is important that the belt be placed in the same position each day, including indexing and belt tightness. Positioning of the belt and abdominal anatomy can be verified using x-ray portals, verification CT scans, and/or onboard CBCT if available. In general, image guidance should be used to ensure that interfraction range variations are less than 3 mm for 95% of the target volume [31]. Additional imaging used for target delineation should employ the same compression as used for the planning CT. For example, if MRI is used for anatomical delineation, an MRI-compatible compression belt should be used. This prevents propagating differences in anatomical positioning caused by the belt. As with any system, patients should undergo training with the appropriate motion management devices to maximize their effectiveness. During simulation, care should be taken to keep devices outside of the potential treatment field.

Accurate registration between imaging sets is important. In addition to bony anatomy, we focus fusions on patient vasculature (celiac and SMA) for unresectable pancreatic head tumors. With breath-hold devices, there is variability in the position of the abdominal target, even with identical tidal volumes. To account for this

reproducibility error, at our institution an additional superior and inferior margin of 2 mm is added to CTV [32, 33].

While pencil beam scanning (PBS) proton therapy can create more conformal dose distributions versus passive scattering techniques, the use of PBS in thoracic and abdominal malignancies has been limited due to the uncertain relationship between spot scanning and respiratory-related anatomical motion [34]. This complicated interplay effect between spot delivery and organ motion has made passive scattering techniques, specifically double scatter or uniform scanning, preferable when treating patients with higher levels of anatomical motion, although PBS is being increasingly adopted for more cases at our institution.

15.3 Target Delineation and Radiation Dose/Fractionation

- The gross tumor volume (GTV) for definitive chemoradiation of borderline or unresectable locally advanced pancreatic adenocarcinoma is drawn on the non-contrast-enhanced, simulation CT scan using the registered contrast-enhanced simulation CT scan and MRI/PET if available to delineate the extent of the gross tumor visible and any involved lymph nodes (≥ 1 cm). On contrast-enhanced scans, pancreatic tumors are often hypodense/hypointense compared to normal pancreatic tissue on the late arterial and venous phases, although they can rarely be isodense/isointense and harder to distinguish from the surrounding parenchyma. To assist with delineation, it can be helpful to carefully look at the biliary anatomy and follow the dilated intrapancreatic biliary duct to the point of obstruction in order to locate tumors in the pancreatic head. Pancreatic tumors often appear as hazy dark-gray soft tissue which can extend into the abdominal fat and duodenum and wrap around the vasculature. Following the celiac and SMA carefully to look for tumor wrapping around these vessels can also help delineate the GTV borders. At our institution we do not electively treat lymph nodes based on data that when prophylactic nodal radiation was omitted, there were few peripancreatic lymph node failures and all were within the 80% isodose line [35]. The CTV is generated by adding a 5 mm margin to the GTV and a PTV by adding 5 mm to the CTV for setup errors.
- Target volumes for pancreatic cancer in the postoperative setting have been well described by consensus contouring guidelines [36]. The clinical target volume is the proximal 1–1.5 cm of the celiac artery, the proximal 2.5 cm of the superior mesenteric artery (SMA), the portal vein (PV) contoured from its junction with the superior mesenteric vein up to the bifurcation of the left and right branches, the pancreaticojejunostomy (PJ), the preoperative tumor volume and surgical bed including any clips left intraoperatively, and the aorta from the most superior structure (PJ, PV, or celiac) down to the level of the L2 vertebral body. Each of these structures is contoured separately with differential expansion to CTV as previously described. These separate CTV structures are then booleaned together into one CTV structure. An ITV is generated from the 4DCT to account for respiratory motion, and then a 5 mm PTV is added (Table 15.1).

Table 15.1 Recommended target volumes and radiation dose ranges (for an RBE = 1.1) for pancreatic and gastric cancers

Clinical scenario	Target	Dose
Definitive chemoradiation for pancreatic cancer	Pancreatic tumor and involved lymph nodes (≥ 1 cm)	5400–5940 cGy
Postoperative chemoradiation for pancreatic cancer	Proximal celiac artery, SMA, PV Pancreaticojejunostomy Preoperative tumor volume Surgical bed/clips Aorta	4500–5400 cGy May boost + margins (5940 cGy)
Adjuvant chemoradiation for gastric cancer	Anastomoses Tumor bed (including clips/gastric remnant) Hepatogastric ligament Lymph nodes <ul style="list-style-type: none"> • Perigastric • Suprapancreatic • Celiac • Cardiac tumors—add L hemidiaphragm, right and left cardiac, pancreatic body, left gastric, and hepatic and celiac arteries • Body tumors—porta hepatic, splenic hilum, pancreatic body, pancreaticoduodenal, left gastric, and hepatic artery • Antrum tumors—porta hepatic, pancreaticoduodenal, pancreatic head 	4500 cGy Consider boost to 5040 (or 5400–5940 cGy for positive margins)
Reirradiation for local recurrence	Gross disease	5400–5940 cGy

- For gastric cancer, a lymph node contouring atlas has been published which nicely describes the anatomic boundaries and contouring of the 16 lymph node stations described in the literature [37]. The CTV includes the anastomoses (esophagojejunal for total gastrectomy and gastrojejunal for a subtotal gastrectomy as well as the duodenal stump), preoperative tumor bed, hepatogastric ligament, and regional lymph nodes. In general lymph node coverage should depend on the location of the tumor within the stomach. For all scenarios we would include the N1 perigastric lymph nodes and suprapancreatic and celiac lymph nodes. For tumors of the *proximal 1/3 of the stomach (cardia)*, we would additionally include lymph nodes along the left and right cardia, the lesser and greater curvature, L hemidiaphragm, and pancreatic body. The left gastric artery, hepatic artery, and celiac artery are also included in the CTV. For tumors of the *middle 1/3 of the stomach (body)*, we would include lymph nodes of the lesser and greater curvature, splenic hilum, porta hepatic, pancreaticoduodenal, and pancreatic body as well as the left gastric artery and hepatic artery. For tumors of the *distal 1/3 of the stomach (antrum)*, we would

Table 15.2 Recommended dose constraints (for an $RBE = 1.1$) to organs at risk for treatment of pancreatic and gastric cancer

Organ at risk	Dose constraints
Kidney (left and right)	$V18 \leq 50\%$
Liver	Mean ≤ 30 Gy
Stomach	$D_{\max} 60, V54 \leq 2\%, V45 \leq 25\%$
Small bowel	$D_{\max} 60, V54 \leq 2\%, V50.4 \leq 5\%, V45 \leq 25\%$
Large bowel	$D_{\max} 60, V54 \leq 2\%, V50.4 \leq 5\%, V45 \leq 25\%$
Duodenum	$D_{\max} 60, V55 \leq 1$ cc, $V54 \leq 5\%$
Spinal cord	Max ≤ 45 Gy

include lymph nodes of the lesser and greater curvature, porta hepatic, pancreaticoduodenal, and pancreatic head lymph nodes. For tumors near the pylorus, we would take an additional distal margin into the duodenum of about 5 cm (Table 15.1).

- Normal abdominal structures such as the liver, kidneys, spinal cord, stomach (for pancreatic cancers), and small and large bowel are contoured as organs at risk. For unresected locally advanced pancreatic cancer, it is important to carefully delineate and contour the duodenum as there can be overlap between the duodenum and target volume (Table 15.2).

15.4 Proton Treatment Planning

Because of the complicated interplay effect between anatomical motion and spot scanning, the majority of pancreatic and gastric cancer patients at our institution have been treated with passive scattering techniques (double scatter or uniform scanning). In select cases where PBS is particularly desirable (e.g., if trying to treat a target with irregular geometry or further spare nearby organs), careful evaluation of anatomical motion is required. A study from our institution investigated the dosimetric impacts of treating abdominal lesions with PBS. It was found that for small motion ($M_{\perp} < 7$ mm and $\Delta WET < 5$ mm, where M_{\perp} is the perpendicular motion amplitude and ΔWET is the change in water equivalent thickness), motion mitigation was not needed. For moderate motion ($M_{\perp} 7\text{--}10$ mm or $\Delta WET 5\text{--}7$ mm), abdominal compression produced a modest improvement. For large motion ($M_{\perp} > 10$ mm or $\Delta WET > 7$ mm), abdominal compression and/or some other forms of mitigation strategies were required [38]. Because of anatomical variability and motion in the abdomen, our institution treats PBS using single-field uniform dose (SFUD) techniques and will be the focus of this chapter. However, future developments in robust optimization may allow for more widespread implementation of intensity-modulated proton therapy (IMPT).

15.4.1 Planning Target Structures

Proton beam range uncertainty due to conversion between CT Hounsfield units and proton stopping-power ratio must always be considered when treating with proton radiotherapy.

- **Passive scattering:** when treating with passive scattering at our institution, this uncertainty is mitigated by adding additional distal and proximal margins to the CTV structure which correct for range uncertainty of 3.5% (of beam range) +3 mm in the distal direction and proximal directions (Fig. 15.5). Lateral margins should also be added to account for motion and setup errors.

Compensator: when using a range compensator to modulate the dose in passive scattering, it is important to use compensator smearing to ensure that the proton beam adequately shapes target volume despite any setup errors and intrafraction motion. At our institution, the smearing parameter is derived from Moyers et al. [39] and is calculated using the following equation:

$$\sqrt{(IM + SM)^2 + \left[0.03 \times (CTV_{\text{depth}} + \text{Compensator}_{\text{thickness}}) \right]^2}$$

where IM is internal motion, SM is setup margin, and CTV_{depth} is the distal depth of the CTV. At our institution we determine internal motion on a patient-specific basis and utilize 3 mm setup error to determine the compensator smearing parameter.

- **Pencil beam scanning:** to account for proton beam range uncertainty in PBS, a planning optimization structure can be created when using a single-field optimization planning technique. At our institution, an optimization structure is created by adding to the CTV a margin of 3.5% of the beam range (accounting for uncertainty in the conversion from Hounsfield unit (HU) values to proton stopping power) plus an additional 1 mm margin (correcting for beam calibration uncertainty). Specific uncertainty values employed should be evaluated on an institutional basis) (Fig. 15.6).

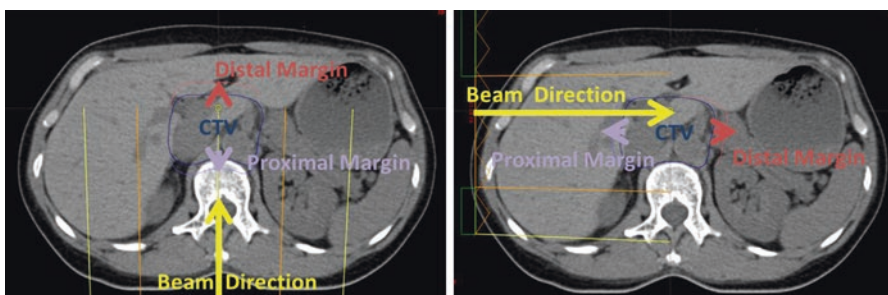


Fig. 15.5 Examples of distal (red) and proximal (purple) margins added to the CTV target along the beam direction for a patient being treated with a posterior beam (left) and right lateral beam (right) using passive scattering proton technique

Fig. 15.6 Pencil beam scanning target volume (PBSTV) optimization (PBSTV) structure (red) is created by adding a margin of 3.5% of the beam range plus 1 mm to CTV structure (blue) in the direction of the beam. A conventional PTV structure (CTV + 5 mm) is shown in green for comparison

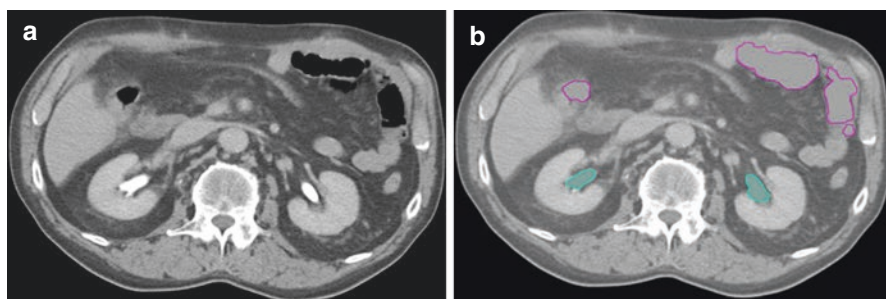
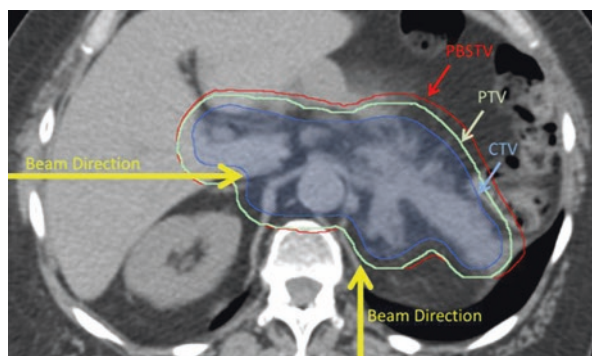


Fig. 15.7 It is recommended that contrast scans be acquired after treatment planning scans. However, if that is not possible, any contrast material appearing in the planning scan which will not be present for treatment should be overridden to the appropriate HU value. Shown are examples of HU material overrides for kidney contrast and bowel gas

15.4.2 Contouring and Overrides

- To account for changes in bowel filling, gas and stool are contoured and assigned an HU value similar to the surrounding tissues. Artifacts created by high-density material should be overridden to an appropriate HU value. It is recommended that contrast scans be performed subsequent to planning CT so that no contrast is present in planning scan; however, if that is not feasible, any high-contrast material that appears in planning scan (e.g., barium) should be assigned an appropriate density or HU value (Fig. 15.7). Manual HU overrides are not required for Volumen contrast.
- If the diaphragm is in close proximity to the target or treatment fields, a diaphragm override volume can be created by adding an additional margin to the diaphragm which is defined by the inferior borders of the lung in the exhale and inhale scans when 4DCT-based planning is employed (Fig. 15.8). The HU value of this margin should be overridden to the value determined by sampling the most superior slice containing the dome of the liver, which generally varies between -50 and $+50$ HUs.

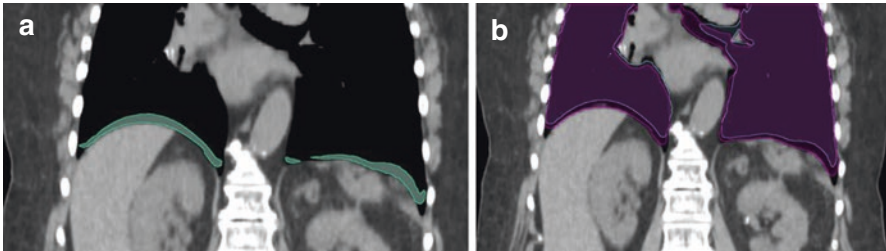


Fig. 15.8 To account for motion of the diaphragm, an additional margin can be added to the diaphragm (a) and is constructed by subtracting the lung contours between the inhale and exhale scans (b) when 4DCT is used for planning purposes

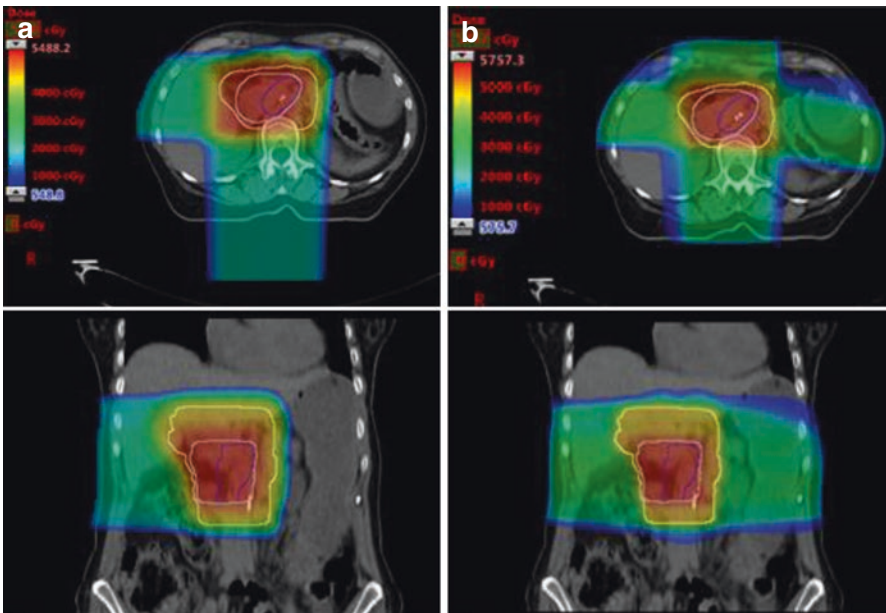


Fig. 15.9 Postoperative radiation for T3 N1 pancreatic adenocarcinoma with a close uncinate margin (4500 cGy to entire postoperative CTV; 5400 cGy to post-op bed, anastomoses, clips, and SMA; and 5940 cGy in region of close margin). (a) Patient was treated with a double-scatter proton plan consisting of a posterior and right lateral beam arrangement to avoid the bowel, stomach, and left kidney. (b) For comparison, an IMRT photon plan is shown. To achieve adequate target coverage in this case, photons deliver higher dose to the stomach, bowel, and left kidney, making protons the more desirable option

15.4.3 Beam Angle Selection

- For both passive scatter and PBS techniques, beam arrangements typically consist of 2–3 coplanar fields, which usually include a posterior beam and either a posterior oblique or right-sided beam (blocking the cord) (Figs. 15.9,

15.10 and 15.11). Gantry angles should be chosen to minimize dose to spinal cord, kidneys, skin overlap, and duodenal dose from the beam penumbra [40]. When using an abdominal compression belt, it is important to override artifacts caused by the belt and attempt to choose beam arrangements which do not shoot through the belt.

- Beams which enter anteriorly or from the patient's left side are avoided due to uncertainties created by presence of air, motion of stomach and bowel, and variability in anterior abdominal tissue.
- If treating with anterior beam arrangements provides a more desirable plan, these beams can be used and possibly given a lower weight (Fig. 15.12). A left-sided beam may be needed when covering left hemidiaphragmatic, perigastric lymph nodes, and splenic lymph nodes for adjuvant gastric cancer cases. The weight of the posterior beam may also be limited by tolerance doses to the kidneys or cord.

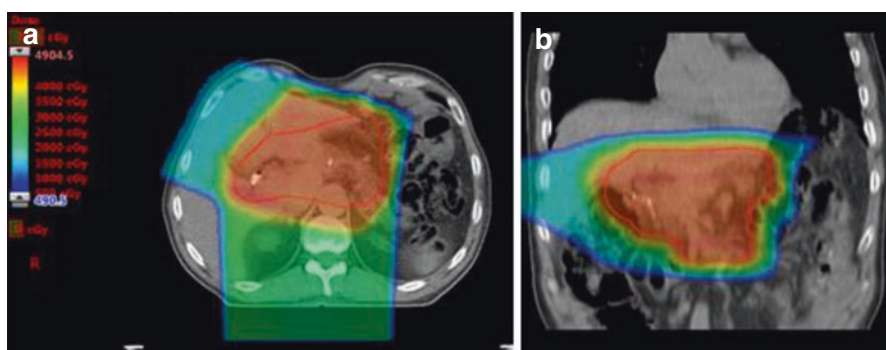


Fig. 15.10 Postoperative radiation for gastric adenocarcinoma in the antrum, treated with double-scatter proton therapy using a posterior and right anterior oblique beam to avoid proton beam traversing through the bowel. Axial (a) and coronal (b) views are shown with PTV shown in red

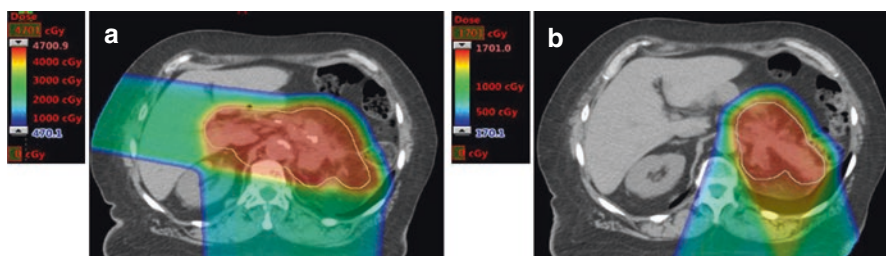


Fig. 15.11 Pancreatic cancer patient (post distal pancreatectomy) with surgical bed recurrence was treated using PBS proton therapy at our institution. (a) To achieve lateral coverage on the right side of the target, a right anterior oblique beam was used with a posterior beam in the plan treated to 44 Gy. (b) Gross residual disease received a conedown to total dose of 60 Gy using right and left posterior oblique beams. In both plans the bowel is almost completely spared, and we avoid treating through variable bowel volume

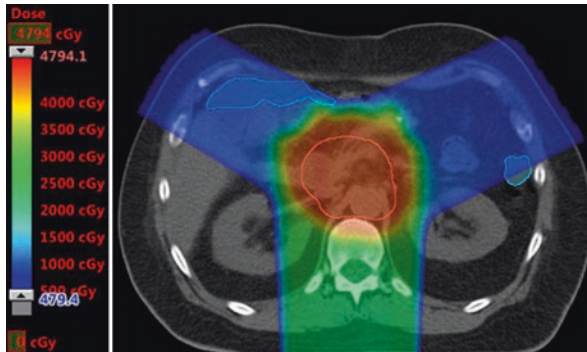


Fig. 15.12 Pancreatic patient treated with double-scatter proton technique using a posterior beam plus two anterior oblique beams. Anterior beams were chosen in this case to minimize kidney dose. To avoid large beam perturbations due to anatomical changes in anterior anatomy (e.g., fluctuations in bowel gas), anterior beams were weighted less than posterior beam (beam weighting of 0.2 for each anterior beam and 0.6 for posterior beam were used)

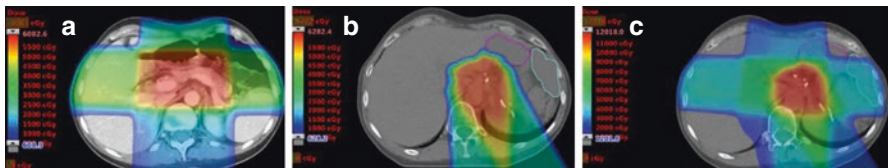


Fig. 15.13 (a) Pancreatic case originally treated with photons after Whipple procedure. (b) Patient had local recurrence which was treated with double-scatter proton therapy using posterior beams to avoid dose overlap of lateral and anterior organs. (c) Sum total of photon and proton treatments indicates higher radiation dose to disease sites and manageable dose to surrounding healthy organs

15.5 Reirradiation

Both PBS and passive scatter techniques can be used for treating pancreatic and gastric malignancies which have received prior radiation to help limit dose to normal tissue that has already been irradiated (Fig. 15.13).

15.6 Dosimetric and Toxicity Comparison

- We have previously reported on a dosimetric study comparing IMRT versus double-scattering (DS) and pencil beam scanning (PBS) proton radiation for unresected pancreatic head cancers [40]. This study demonstrated that both DS and PBS decreased duodenum, stomach, and small bowel dose in the low-dose region. The V20 Gy to the stomach was reduced from about 20% with IMRT to 10% with proton beam radiation, and for the small bowel, V20 was 6.5% with PBS, 9.8% with DS, and 19.7% with IMRT. However, dose to the duodenum, stomach, and

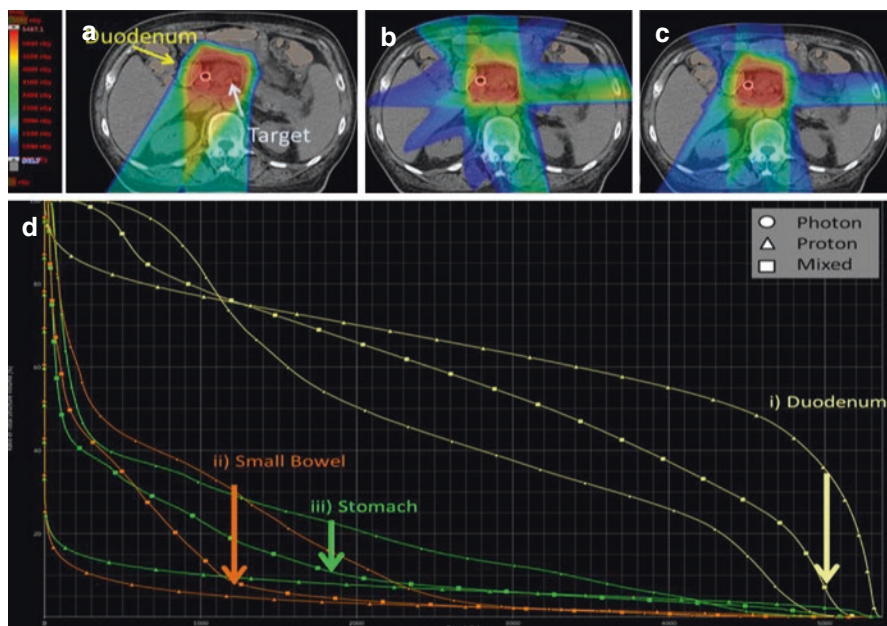


Fig. 15.14 (a) In some cases, a proton plan (using posterior and right posterior oblique beams) may result in a larger volume of tissue going to D_{\max} in critical organs near the PTV or if overlapping the PTV (e.g., the duodenum). (b) An IMRT plan may decrease the volume of high dose to the OAR due to increased conformality, at the expense of increased low-dose spread to other OARs. (c) A combined proton (*double-scatter*)/photon plan was administered to this patient to achieve an optimal balance between high- and low-dose sparing. (d) DVH comparison for photon-only plan (*circle*), proton-only plan (*triangle*), and mixed proton-photon plan (*square*). In this case, the benefit of a mixed proton-photon plan included significant decrease in (i) high dose to duodenum versus proton-only plan, (ii) low dose to small bowel versus photon-only plan, and (iii) low dose to stomach versus photon-only plan

small bowel in the high-dose region (>40 Gy) showed IMRT to be superior followed by PBS and finally DS. This study highlighted that in unresected pancreatic head tumors, in close proximity to or invading the duodenum, there is a need for high conformality which may not be met by DS or PBS plans alone. The quality of life and toxicity outcomes for this comparison have not yet been evaluated. It is unknown how a large volume of duodenum/stomach/small bowel getting a low-dose bath from IMRT may impact the toxicity or quality of life of patients compared to a mid- to high-dose point near the tumor as long as maximum dose constraints to OARs are met. As our proton beam radiation techniques advance and we improve motion management techniques as previously described and begin to utilize IMPT, we may potentially achieve the optimal combination of high conformality combined with minimal integral dose to nearby OARs. In the meantime, our institution has routinely used mixed photon/proton plans to decrease the volume of duodenum in the high-dose region while still achieving lower integral dose to the abdomen than a photon plan alone (Fig. 15.14).

- A unique and rare presentation of pancreatic cancer is the local-regional recurrence, with or without minimal metastatic burden. These tumors may be characterized by intact expression of SMAD4 [3]. We have previously enrolled patients with locally recurrent pancreatic adenocarcinoma on a proton beam reirradiation registry and reported on 15 of these patients [41]. Proton reirradiation was generally well tolerated with a median survival of 15.7 months and minimal grade 1 and 2 non-hematologic acute toxicities, grade 3 fatigue in 2 patients, and no grade 2 or higher late toxicities [41]. There was one duodenum ulceration in a patient treated to progression of unresected locally advanced adenocarcinoma with duodenum abutting the PTV. We recommend patients are treated to the gross disease alone with minimal CTV expansions (the median CTV in our reirradiation cohort was 71 cc) and try to avoid beam angles which overlap with the prior radiation fields.

15.7 Patient Positioning, Immobilization, and Treatment Verification

Treatment positioning should be performed using the same immobilization techniques as used in simulation. Localization should be performed daily by matching bony anatomy in orthogonal x-ray imaging. If volume of stomach will impact treatment delivery, oral contrast can be administered to more clearly delineate gastric volume in kV imaging. If available, onboard volumetric imaging (CBCT) can be used to verify soft tissue anatomy. For proton patients we perform biweekly verification scans to check for changes in anatomy, such as weight loss, and variation in bowel gas and gastric filling.

15.8 Discussion and Future Developments

- The utilization of protons for treating pancreatic and gastric cancers can be useful to decrease integral dose to stomach, bowel, kidney, and liver depending on the location of the PTV and beam arrangement chosen. In the case of adjuvant chemoradiation for resected pancreatic and gastric cancers, where field sizes are often large, proton radiation can reduce dose to OARs sparing kidney, liver, and a large amount of bowel, improving the toxicity profile. Advances in co-registration software for image fusions, incorporating cone beam CT into IGRT for proton delivery, gating for motion management, and better understanding of the range uncertainty (allowing margins to be decreased) would help us advance proton planning and treatment.
- Delivering radiation with limited motion (e.g., using breath hold) is of great importance as it allows delivery of higher doses to target, lower doses to OARs, and more treatment reproducibility. Motion management is particularly important with proton therapy and truly critical with PBS.

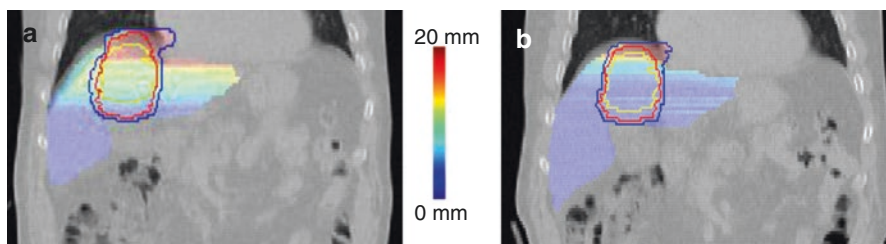


Fig. 15.15 Figure showing the difference in motion without (a) and with (b) abdominal compression. Difference of CTV (yellow), ITV (red), BSPTV (blue), and Δ WET (color wash) over CT images (Figure courtesy of Liyong Lin's oral presentation at the AAMP meeting, 2016)

- Further investigation of motion mitigation techniques will likely make treating with PBS more clinically feasible. Studies at our institution have utilized abdominal compression to decrease motion for the treatment of liver tumors with PBS [38, 42]. Abdominal compression resulted in reduction of the beam-specific PTV (PBSTV)/CTV and ITV/CTV volume ratios, less overlap of BSPTV with heart, and a clear reduction of motion, thus less variability in water equivalent thickness (WET) traversed by the proton beam. When PBS plans utilizing abdominal compression were analyzed using 4DCT for ten patients being treated to a liver tumor, this method resulted in decreased mean liver dose, smaller ITV and PBSTV margins, and a reduction in motion amplitude. Although this study focused on liver patients, the implications and conclusions can be similarly applied when treating other abdominal targets (Fig. 15.15).
- Utilizing proton beam radiation for unresected pancreatic cancer can be challenging due to larger volumes of the duodenum which may be included in the high-dose region of the PTV. Combination photon/proton plans can be used to reduce the volume of the duodenum treated to high dose, reduce the volume of the stomach and bowel in the low- to intermediate-dose range, and decrease overall integral doses. In the future, the use of PBS with abdominal compression, cone beam CT, and IMPT may allow for improved conformality and decreased margins near the duodenum.

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