Introduction

Pancreatic cancer accounts for about 3% of all cancers in the US, and accounts for about 7% of cancer deaths (American Cancer Society). An estimated 48,960 new cases of pancreatic cancer are expected in the US in 2015 (cancer Facts & Figures 2015. www. Cancer.org). Surgery, radiation therapy, and chemotherapy are treatment options that may extend survival and/or relieve symptoms in many patients. For all stages combined, the 1- and 5- year relative survival rates are 28% and 7%, respectively (cancer Facts & Figures 2015. www. Cancer.org) [1].

The majority of pancreatic cancer patients have locally advanced or metastatic disease [2]. Chemoradiotherapy is an important treatment technique of locally advanced pancreatic cancer. It can be delivered as adjuvant or neoadjuvant treatment [3]. A qualitative systematic study reviewed 21 studies as follows: two meta-analyses, 13 randomized trails, and six nonrandomized trials [4]. The study concluded that the chemoradiotherapy increases overall survival when compared with best supportive care or with exclusive radiotherapy, but is more toxic. Chemoradiotherapy is not superior to chemotherapy in terms of survival and increases toxicity. Recent data favor limited irradiation to the tumor volume. Fluorouracil is still the reference chemotherapy in association with radiotherapy. Radiotherapy with concurrent continuous 5-fluorouracil infusion increased the length and quality of survival as compared to no chemoradiotherapy in patients with locally unrespectable pancreatic cancer [5].

Chapter 2

Radiation Therapy for Pancreatic Cancer

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evaluated the role of radiation therapy with concurrent gemcitabine (GEM) compared with GEM alone for localized unrespectable pancreatic cancer and concluded that the addition of radiation oncology to GEM improved the overall survival with acceptable toxicity [6].

Local failure continues to be a major problem in the management of pancreatic cancer. Delivery of adequate radiation doses to the pancreas is limited by the tolerances of the adjacent normal structures. Conventional radiotherapy techniques with conformal 3-D, intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and intraoperative radiation therapy are options to deliver adequate radiation for local control. Acute and late gastrointestinal toxicity can be reduced by imaging strategies and respiration control.

**Imaging Techniques**

Computed tomography (CT) scan with a contrast is a common procedure in radiotherapy (RT) planning for target definition in pancreatic cancer patients. The CT scan can be acquired in free-breathing or breath-hold to reduce the motion artifacts. Usually, adequate margin is added around the target to account for motion of the tumor or to avoid missing parts of the tumor. A respiratory-gated four-dimensional CT (4D-CT) technique is an alternative technique to capture the motion of the target at different breathing phases. Usually, ten CT data sets are acquired to capture a complete breathing cycle. The 4D-CT data sets can be used later, after reconstruction, to generate multiple CTs to reflect the target average, minimum, and maximum positions. Contrast enhanced (CE) 4D-CT has been implemented in radiotherapy to improve the definition of the pancreatic, which allows the physician to use a patient-specific target volume definition and avoid irradiating unnecessary normal tissue [7,8]. Other imaging techniques such as positron emission-computed tomography (PET-CT) and magnetic resonance (MR) can be registered with the radiotherapy CT to help defining the tumor but such registration may suffer from the errors associated with the registration. Simultaneous multimodality imaging systems can resolve the registration errors and provide a superior solution to define the target volume.

**Radiotherapy Techniques**

Conventional radiotherapy should be fractionated to avoid toxicity. 1.8-2 Gy/fraction to a total dose 50-55 Gy is recommended. Hypofractionation regimen (30 Gy in 10 fractions) was used safely by MD Anderson cancer center group [9]. Dose can be delivered with either 3D-conformal or Intensity Modulated Radiation Therapy (IMRT) techniques. IMRT for pancreatic cancer was found to be superior to three-dimensional conformal radiation therapy (3-D CRT) in decreasing toxicities. Compared to 3-D CRT, IMRT reduced the mean dose to the liver, kidneys,
stomach, and small bowel and reduced the delivery of above-threshold doses to these structures [10]. A potential concern with IMRT for pancreatic cancer is that IMRT delivery could increase small bowel toxicity by increasing the exposure to low-dose radiation therapy (RT). IMRT effect on the small bowel was compared to 3-D CRT by delivering a prescription dose of 61.2 Gy to the gross tumor volume (GTV) and 45 Gy to the clinical treatment volume (CTV) [11]. IMRT plans were more conformal than 3-D-CRT plans and the average dose delivered to one third of the small bowel was lower with the IMRT plan [11]. Another study analyzed 3-D CRT, sequential boost IMRT, and integrated boost IMRT and concluded that the Planning target volume (PTV) was comparable among the three techniques but the 3-D CRT exceeded small bowel tolerance in some patients and none of the IMRT plans exceeded tissue tolerance at any described dose [12].

A comprehensive review study of all the IMRT studies indexed in PubMed/Medline with recent 3D-CRT trials and concluded that IMRT reduced treatment-related toxicities but no significant changes in progression-free survival or overall survival [13].

Stereotactic body radiation therapy (SBRT), as an adjunct or alternative technique to conventional radiation techniques. SBRT offers the potential for radiation dose escalation and retreatment over a short period of time. Stanford University (Stanford, CA) established a 25 Gy single fraction SBRT technique with systematic therapy to treat pancreatic cancer [14-17]. In a phase II study from the same group, 45 Gy IMRT with concurrent 5-FU followed by a 25 Gy SBRT boost regimen was used with pancreatic cancer [16]. Mid-breathhold and respiratory techniques were used. Rate of control in this study was excellent but no significant impact on the overall survival rate. Gastrointestinal (GI) toxicities is a concern with SBRT technique and should be evaluated carefully. Breath-hold or respiratory tracking can significantly reduce toxicity by using small margins around the target. Dose escalation to the target volume using simultaneous integrated boost was also reported in a phase I study to increase the local control [18]. In this study, a dose of 44.25 Gy in 15 fraction was delivered with dose escalation stopped at 58 Gy.

Volumetric Modulated Arc Therapy (VMAT) is comparable to static beam IMRT technique and can deliver the dose faster [19]. VMAT with SIB was used to treat pancreatic cancer with single arc to deliver 54 Gy with daily imaging [20]. The VMAT with SIB showed excellent tumor coverage while sparing the organs at risks.

Electron-beam intraoperative radiation therapy (IORT) was used to irradiate the bed of the resected pancreas to improve local control [21,22]. Survival probability did not differ among patients using IORT or external beam radiation therapy but IORT improved the local con-
Motion Management

Reduction of the planning target volume (PTV) margins, imaging strategies, and respiration control can be used to reduce the acute and late gastrointestinal toxicity. Organs in the upper abdomen can exhibit a significant respiration-induced movement which can compromise the target coverage and exceed the dose tolerances to normal tissues. Using dynamic magnetic resonance imaging, the largest movement was noticed in the cranio-caudal direction due to the movement of the diaphragm for pancreas and liver [24]. In another study using two MRIs for pancreatic cancer patients, the largest tumor motion was in the cranio-caudal direction and the least motion was in the lateral direction [25]. The end exhale position was the most stable position in the breathing cycle and tumor spent more time closer to the end exhale position than to the end inhale position [25].

Motion of the pancreatic tumors is highly variable between patients and it can exceed the GTV margins accounted for. The margins used for irradiating pancreatic tumors have varied from 0.5 to 2.5 cm [10-12,26,27]. Treatment plans using fiducials or surrogates for tumor tracking should be considered and used with caution as the deformation with breathing, and motion of margins does not correlate well with abdominal wall or diaphragmatic motion [28]. Several approaches to optimize the delivery of radiation to pancreatic cancer using a breath hold (BH) approach or by synchronizing the radiation to the breathing cycle using external markers or a spirometer.

Organ motion due to respiration can be quantified by several methods, including fluoroscopy, ultrasound (US), MRI, CT and PET. Respiratory corrected 4D-CT is the method of choice for motion characterization in radiation therapy. The 4D-CT uses an external respiratory signal from Varian Real-Time Position Management system (RPM, Varian Medical Systems, Palo Alto, CA) or Philips respiratory air bellows (Philips Medical system, Eindhoven, The Netherlands) to correlate with individual CT scans. This approach allows the physician to watch the movement of the target with respiration and chose adequate margin to ensure coverage of the target at the full extents of motion. An average intensity projection CT (AIP-CT), maximum intensity projection CT (MIP-CT), and minimum intensity projection CT (MIP-CT) can be generated from the 4D-CT scans and used for contouring and/or treatment planning.

Irregular breathing, correlation between external and internal motions, resorting artifacts, and poor soft-tissue contrasts are challenges for abdominal organs [29,30]. MRI provides a superior soft-tissue contrast and was used by many investigators to quantify the tumor motion. 4-D MRI have been used by multiple investigators. Cai et al
introduced a 4-D MRI protocol using fast 2D cine-MRI imaging sorted by respiratory phase. Tryggestad et al [32] have developed a longer-duration MRI and post-processing technique to derive the average of mobile anatomy. Hu et al [33] generated 4-D MRI image based on 2D acquisition using navigator triggered image acquisition at preselected respiratory amplitudes. Stemkens et al [34] used surrogate signals and MR sampling techniques to reconstruct the 4-D MRI by resorting 2D k-space data. All the previous studies suffered from stitching artifacts and anisotropic resolution. Yang et al [35] used a self-gating k-space sorted 4-D MRI method to overcome the limitations from the previous studies but their images were noisy.

**Treatment Delivery**

Respiration can influence the delivery of radiation treatment for pancreatic cancer patients. An ultrasonic pancreatic study showed excursions ranged from to 3.5 cm [36]. Another study using MRI to study the respiration-induced movement for upper abdominal organs reported 23.7±15.9 mm movement in the cranio-caudal direction [24]. A newer MRI study reported a tumor motion in craniocaudal direction with average peak-to-peak amplitude of 15 mm (range 6–34 mm), in the anteroposterior direction was on average 5 mm (range 1–13 mm), and in the lateral direction was on average 3 mm (range 2–5 mm) [25]. Several approaches have been described to treat organs effected by breathing motion such as breath-hold, gating using external markers, and gating using internal markers. Pancreas is most stable and spent more time closer to the end of the exhale position so gated delivery best performed around the end of exhale position [25]. A patient-specific internal target volume should be based on 4D-CT for gated and non-gated treatment. The 4D-CT is acquired under regular free breathing using Varian RPM or Philips air bellows systems. The 4D-CT are usually reconstructed into separate 3D-CT scans based on the number of respiratory phases (0%-90%) to assist in contouring and GTV margins. To reduce GTV margins and improve the tolerance of treatment, free-breathing gating or breath-hold treatment should be considered. Daily breath-hold kV-CBCT at end-exhalation with visual feedback was used to treat patients with pancreatic cancer using IMRT [37]. Setup was based on bony anatomy and residual errors were recorded. The study concluded that target matching is required to correct for interfraction motion.

Yorke et al. [29] used pneumatic compression and kilovoltage images acquired every 5-6 seconds to assess the intrafractional motion of GI tumors with implanted fiducials and SBRT planning. They concluded that Pneumatic compression associated with fiducial based IGRT were effective in preserving the coverage of the target.
Interfractional and Intrafractional

Target deformation is substantial with breathing, and tumor border position does not correlate well with abdominal wall or diaphragmatic position so external markers for motion management may not account fully for tumor motion and should be used with caution [28]. Gating around the end-exhalation reduced the GTV motion by 46% to 60% and GTV displacement was associated with RPM, the biliary stent and fiducials seeds but better correlation was with the biliary stent and fiducials seeds as reported by Huguet et al [38].

Several studies used various IGRT techniques to assess and reduce pancreatic tumor interfractional motion by aligning to the implanted markers after bony alignment. Kilovoltage (kV) cone beam computed tomography (CBCT), megavoltage (MV) CBCT, and orthogonal kV planar imaging are IGRT options used with a reference CT to align the patient. Solla et al. [39] assessed the interfractional motion for 10 pancreatic patients using weekly megavoltage (MV) cone beam computed tomography (CBCT) images and the position of a single fiducial marker. Whitfield et al. [40] used kilovoltage (kV) CBCTs in order to calculate the interfractional fiducial motions after bony alignment for 13 patients. Jayachandran et al. [41] used seeds and orthogonal kV planar imaging for five patients in order to quantify the interfractional variations in pancreatic tumor motion. Van der Horst et al. [42] quantified the interfractional pancreatic position using fiducial markers and CBCT. They also looked at the migration of the markers with time and concluded that the markers can migrate so it is recommended to align to the fiducial markers rather than the bony anatomy. The reference CT for daily alignment can be either free breathing CT (FBCT) or AIP-CT. If the FBCT is used as the reference CT for IGRT, after correcting for the setup errors with bony alignment, the alignment to the implanted markers can introduce a systematic errors because markers on FBCT represents a snap shot of the breathing cycle. If AIP is used as the reference image for IGRT, after correcting for the setup errors with bony alignment, the alignment to the implanted markers will be more accurate as the markers in this CT set are captured at the average breathing position [43].

Figure 1: Differences in COM coordinates between (a) FBCT vs. CBCT; (b) AIP vs. CBCT, (c) FBCT/CBCT vs. AIP/CBCT. Vertical error bars represent the standard deviations [43].
Figure 2: Changes in the PTV coverage and normal structure sparing for a single case resulted from using the markers on the FBCT (solid curves) versus the markers on the AIP (dashed curves) for IGRT[43].

Amoush et al. [43] studied the systematic uncertainties resulted from using the FBCT or AIP as a reference CT for IGRT. The systematic uncertainties after bony alignment are shown in Figure 1 between center of masses (COMs) coordinates of (a) FBCT versus CBCT, (b) AIP versus CBCT and (a)-(b). The shifts in the implanted marker’s COMs between FBCT and CBCT included the interfractional tumor displacement, the potential systematic uncertainties of the COMs of the markers, and the residual bony registration uncertainties. The shifts in the COMs of the implanted markers between AIP and CBCT included the interfractional tumor displacement and residual bony registration. CBCT represents the average breathing motion of the patient, and the use of AIP as a reference image set is recommended to reduce the uncertainties observed in FBCT. If FBCT is used as a reference image, additional uncertainties need to be considered [43]. Figure 2 shows the reduction PTV100% coverage resulted from using the FBCT implanted markers as the reference for IGRT [43].

Conclusions

Radiotherapy with concurrent chemotherapy increased the length and quality of survival as compared to no chemoradiotherapy in patients with locally unresectable pancreatic cancer. External or intraoperative radiotherapy techniques can be used for radiotherapy for local control. SBRT or SIB are other options to deliver higher radiation in shorter time. Contrast enhanced 4D-CT for simulation provides comprehensive information to define the tumor and use a patient-specific margins to ensure adequate coverage to the target without exceeding the dose tolerances of normal structures. The AIP generated from 4D-CT reflects the average position of the target and should be considered for treatment planning. Implanted fiducial markers along with IGRT techniques can reduce the interfractional errors. Using the AIP as reference for IGRT is recommended to reduce systematic uncertainties. Gated radiotherapy using either external or internal markers can be considered to minimize the intrafractional motion of the pancreatic cancer but external markers can provide poor correlation with the motion of the target.
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