Gastrointestinal Cancer: Pancreas

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1 Introduction

Despite advances in surgical management and the use of multimodal therapy with chemotherapy and radiotherapy, pancreatic cancer continues to be an uncommon yet highly lethal malignancy. In the United States, the American Cancer Society estimated 53,070 new cases of pancreatic cancer and 41,780 deaths in 2016, making pancreatic cancer the 12th most common cancer and the 3rd leading cause of cancer-related death (American Cancer Society 2016). Thus, pancreatic cancer has a disproportionately high mortality rate with a 5-year overall survival of <6%. The term pancreatic cancer typically refers to pancreatic ductal adenocarcinoma, which is a disease of exocrine ductal glands that comprises 85% of pancreatic malignancies (Geer and Brennan 1993). Non-hereditary risk factors for development include cigarette smoking, high body mass index, and chronic inflammation in the setting of chronic pancreatitis

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(Lowenfels and Maisonneuve 2006; Michaud et al. 2001; Stolzenberg-Solomon et al. 2008). The majority of neoplasms arise from the head of the pancreas, and common presenting symptoms include epigastric pain, jaundice secondary to obstruction, and weight loss in the setting of malabsorption and endocrine dysfunction (Porta et al. 2005). Following biopsy and histologic confirmation, staging is determined through dedicated thin-sliced computed tomography (CT) of the pancreas with triple-phase contrast enhancement to visualize disease extent and vessel involvement. The American Joint Committee on Cancer staging system is based on primary tumor (T), regional lymph node (N), and distant metastasis (M) staging; however, the National Comprehensive Cancer Network (NCCN) and a number of institutions frequently utilize a staging system which stratifies patients by resectability (American Cancer Society 2009; Tempero 2016). The NCCN staging reflects the extent of disease in terms of surgical resectability as resectable, borderline resectable, locally advanced (unresectable), and metastatic. This resectability-based staging is primarily determined by the presence of distant metastases, tumor involvement of adjacent structures, and tumor relation to arterial (the celiac axis, hepatic artery, and superior mesenteric artery) and venous (the superior mesenteric vein and portal vein) structures (Tempero 2016). While surgical resection remains the cornerstone of definitive therapy, 80% of patients present in more advanced, unresectable stages and, as a result, multidisciplinary care plays a critical role in determining both definitive and palliative treatment options.

2 Overview

2.1 Surgical and Chemotherapy Management

Surgery remains the mainstay of definitive treatment, and achieving resection with negative margins is currently the only potential curative option. Surgery for head-of-the-pancreas tumors consists of a classic pancreaticoduodenectomy (Whipple procedure), which involves resection of the head of the pancreas, a portion of the duodenum, proximal jejunum, common bile duct, gallbladder, and a partial gastrectomy. Modifications to the classic Whipple include the pylorus-preserving pancreaticoduodenectomy, and subtotal stomach-preserving pancreaticoduodenectomy. Body- and tail-of-pancreas neoplasms represent the minority of surgically eligible candidates, as few are detected prior to metastases. Surgical management for these cases consists of either a total pancreatectomy (some body lesions) or a distal subtotal pancreatectomy. Some of these cases are now being performed with a laparoscopic or robotic approach with decreased morbidity, thus allowing a more rapid initiation of adjuvant therapy (Wolfgang et al. 2013).

Even after surgery with complete tumor removal, the majority of pancreatic cancer patients ultimately succumb to disease and 5-year overall survival remains at 10–30% (Tempero 2016; Yeo et al. 1995; Cameron et al. 1993; Balcom et al. 2001; Kang et al. 2014). Long-term survival is achieved in a small subset of patients, and favorable prognostic factors include resection with negative margins, node-negative resection, small and well-differentiated tumors, and completion of the operation at high-volume pancreatic centers (Geer and Brennan 1993; Cameron et al. 2006; Yeo et al. 1997). However, the majority of pancreatic cancer patients present with advanced disease and are considered unresectable due to encasement of critical and non-reconstructable vasculature or due to metastatic disease. As such, a minority of patients are eligible for resection at diagnosis and multidisciplinary management is needed (Pawlik et al. 2008).

Chemotherapy plays a significant role in the management of pancreatic cancer, as the natural history is dominated by rapid progression to metastatic disease. Systemic therapy provides improved quality of life as well as prolonged survival, and key determinants in chemotherapy choices include goals of care, performance status, hepatic function, and renal function

(Tempero 2016). First-line therapy consists of single-agent gemcitabine as well as combination regimens such as gemcitabine and albumin-bound paclitaxel and FOLFIRINOX (leucovorin, infusional fluorouracil, oxaliplatin, irinotecan). While combination regimens have prospectively been shown to correlate with improved survival compared to gemcitabine alone in patients with metastatic disease, combination regimens are also associated with higher treatment-related morbidity that leads to intolerance in poor-performance-status patients (Ychou et al. 2007; Ueno et al. 2016; Poplin et al. 2016). Thus, goals of care, performance status, and patient preferences play a significant role in systemic therapy decision-making. Additionally, chemotherapy is used in the adjuvant setting to prevent local and distant recurrence in patients who undergo resection. Despite surgical resection with negative margins, even early-stage tumors have a propensity for developing metastatic disease in the lung, liver, and peritoneum as well as a local recurrence within the resection bed (Griffin et al. 1990; Tepper et al. 1976). In chemo-naïve patients who undergo surgical resection, there is category I evidence for adjuvant gemcitabine monotherapy based on the disease-free and overall survival benefit reported in the CONKO 001 trial (Oettle et al. 2013). A combination of 5-fluorouracil (5-FU)/leucovorin is another adjuvant category I option that has demonstrated similar survival outcomes to adjuvant gemcitabine in ESPAC-3 (Valle et al. 2014). The role of adjuvant chemoradiation therapy (CRT) remains controversial, but 5-FU or gemcitabine is commonly used in combination with radiation as a radiosensitizer (Regine et al. 2011; Neoptolemos et al. 2009). Finally, in borderline and locally advanced disease, there is an evolving role in utilizing neoadjuvant therapy to downstage disease with the goal of achieving a curative-intent resection. Clinical practice varies and regimens including FOLFIRINOX and gemcitabine + albumin-bound paclitaxel are typically recommended for 2–6 months prior to initiation of radiation therapy (Tempero 2016; Small et al. 2016; Jones et al. 2017; Coveler et al. 2016; Balaban et al. 2016).

2.2 Radiotherapy and Hypofractionated Radiation in Pancreatic Cancer

Radiation therapy is utilized for definitive and palliative management in pancreatic cancer and its clinical utility has been explored in all stages of disease. Radiotherapy is used to improve local control adjuvantly in resectable disease, neoadjuvantly in borderline resectable and non-metastatic locally advanced disease, definitively in unresectable locally advanced disease, and palliatively in select patients with metastatic disease. The benefit of adjuvant radiation following surgical resection is controversial and is being evaluated in the cooperative RTOG 0848 trial where patients are being randomized to chemotherapy alone or chemotherapy followed by CRT. Historically, radiation therapy in pancreatic cancer has been dominated by a conventionally fractionated CRT regimen of 45–54 Gy in 1.8–2 Gy fractions. However, conventionally fractionated regimens consisting of 5–6 weeks of daily therapy are associated with toxicity that often limits patients' ability to tolerate additional full-dose systemic therapy and offers limited effectiveness in both adjuvant and locally advanced disease.

Recently, there has been a rise in clinical trials investigating the role of hypofractionated therapy and stereotactic body radiation (SBRT), particularly in locally advanced pancreatic cancer patients. The critical importance of local control in pancreatic adenocarcinoma is seen in surgery, as complete surgical resection with negative margins is the only potential means of long-term survival. Given the poor survival outcomes in non-metastatic, unresectable disease despite chemotherapy and radiation, several trials have explored the use of SBRT to provide ablative biologic effective doses with curative intent. SBRT regimens involve highly conformal, high-dose-per-fraction radiation delivered in 1–5 fractions. SBRT is prescribed to lower isodose lines to allow for conformal treatments, promotes safety due to sharp dose fall-off near critical structures, and also provides dose heterogeneity within the

planning target volume (PTV) (Myrehaug et al. 2016). SBRT in 3–5 fractions offers a number of clinical benefits including new data demonstrating local control, reduction of pain and improvement in quality of life, minimal toxicity, and reduced interruption of systemic regimens (Moningi et al. 2015a, b; Herman et al. 2015a). Moreover, recent exploration of neoadjuvant SBRT in borderline and locally advanced disease has been associated with increased rates of margin-negative resection for patients who are ultimately able to undergo resection (Moningi et al. 2015b).

However, pancreatic cancer, and head lesions in particular, is often in close proximity to a number of critical structures, namely the stomach, duodenum, and small bowel. As these are serial gastrointestinal structures, which result in significant toxicity or functional impairment when damaged, they represent significant dose-limiting organs at risk. Therefore, the ability to further escalate the dose of pancreas SBRT is likely reliant on radiation sensitizers to increase tumor response and/or radiation protectors to decrease treatment effect of the duodenum/stomach.

3 The Role of Radiotherapy in Locally Advanced Disease

While the natural history of locally advanced pancreatic cancer is dominated by metastatic disease, local progression significantly contributes to morbidity as well as mortality (Crane 2016). In an autopsy series, 30% of pancreatic patients died of locally destructive pancreatic cancer, and local failure has been reported as first site of failure in 58% of patients even with conventionally fractionated radiation (Iacobuzio-Donahue et al. 2009; Gastrointestinal Tumor Study Group 1985). Thus, while managing systemic disease is certainly critical in locally advanced pancreatic cancer, improving local control can offer symptom relief and improve quality of life, reduce local recurrence rates, and may prolong survival if coupled with effective systemic therapy. After all, local control with surgery is potentially curative in a subset of patients, and the ultimate goal would be to optimize the use of radiotherapy to achieve long-term survival.

3.1 Conventionally Fractionated Chemoradiation in Locally Advanced Pancreatic Cancer

Historically, chemotherapy and consolidative radiation have been used in patients with non-metastatic, locally advanced pancreatic cancer (Moertel 1969; Moertel et al. 1981). However, due to the propensity for locally advanced pancreatic cancer to metastasize and considering evidence from several key randomized trials, the practice of routinely adding conventionally fractionated (CRT) to systemic therapy is in question (Gastrointestinal Tumor Study Group 1988; Chauffert et al. 2008; Loehrer et al. 2011; Klaassen et al. 1985; Hammel et al. 2016). Multiple prospective randomized trials sought to evaluate the benefit of the addition of radiation to systemic therapy with conflicting results (Gastrointestinal Tumor Study Group 1988; Chauffert et al. 2008; Loehrer et al. 2011; Klaassen et al. 1985; Hammel et al. 2016). The Eastern Cooperative Oncology Group (ECOG) 4201 compared gemcitabine alone vs. CRT using a standard RT dose of 50.4 Gy with concurrent gemcitabine (Loehrer et al. 2011). The CRT arm was associated with improved overall survival, but the cost of this survival benefit was increased grade 3–4 gastrointestinal toxicity. However, while there was a statistically significant improvement in survival, it is of note that the trial closed early due to poor accrual, decreasing statistical power. While ECOG 4201 favors a CRT approach, another recent trial, the FFCD-SFRO study, found a survival benefit in patients who received gemcitabine alone without CRT (Chauffert et al. 2008). Patients randomized to the CRT arm received 60 Gy in 30 fractions to a large radiation field coupled with an intensive chemotherapy regimen comprised of infusional 5-FU, intermittent cisplatin, and

maintenance gemcitabine. Only 42% of patients in the CRT arm were able to complete the full treatment regimen due to intolerance of the intensive multi-agent chemotherapy regimen. Additionally, it is difficult to discern what clinical benefits or harms were due to the radiation given the significantly different chemotherapy regimens between the two arms. Finally, data from the largest and most recent prospective trial investigating CRT in locally advanced pancreatic cancer come from the LAP-07 trial (Hammel et al. 2016). Patients were initially randomized to 4 months of induction gemcitabine or gemcitabine plus erlotinib. This was followed by a second randomization to consolidative CRT (54 Gy, three-dimensional conformal radiation [3D-CRT] delivered concurrently with capecitabine) for patients who were free of systemic progression. Patients who received CRT had prolonged local progression-free survival, increased time between first-line and second-line chemotherapy, and no increase in grade 3–4 toxicity with the exception of nausea. However, there was no overall survival benefit for patients who were treated with CRT (10.1 months vs. 12.7 months from the second randomization) (Hammel et al. 2016). One factor which limits interpretation of the role of radiation in this trial is that only 37% of patients were treated with radiation per protocol, with 21% having major deviations and 50% having minor deviations in their radiation treatment plan. Thus, despite the historic use of consolidative radiation with chemotherapy in locally advanced pancreatic cancer, recent clinical trials have not resulted in a clear consensus. There were modest overall survival benefits associated with radiation in ECOG 4201 and a superior local progression-free survival in LAP-07. However, patients ultimately succumb to both progression and metastatic disease. It may be that the benefit of local control is not appreciable without improved systemic regimens, and published trials to date have not used more contemporary regimens such as FOLFIRINOX or nab-paclitaxel/gemcitabine. In spite of the conflicting evidence, it is clear that the prognosis for locally advanced pancreatic adenocarcinoma remains poor and requires further investigation.

3.2 SBRT in Locally Advanced Pancreatic Cancer

SBRT and hypofractionated radiation use higher doses per fraction to optimize the ablative tumor effect. A summary of clinical trials evaluating SBRT can be found in Table 1. The feasibility of using SBRT in LAPC was initially used in a dose escalation trial involving up to 25 Gy in one fraction reported by Koong et al. at Stanford University in 2004 (Koong et al. 2004). All patients enrolled on the trial had metastatic progression as the first site of progression, the primary objective of evaluating local control was achieved, and the trial was stopped early before any dose-limiting toxicity was observed. Not only did this trial demonstrate that SBRT could potentially be a well-tolerated and effective means of local control, but it also illustrated the importance of the use of systemic therapy. Integrating chemotherapy prior to SBRT not only allows for better control of micrometastatic disease, but its up-front use may be a means of screening out patients who will fail distantly and thus be less likely to benefit from SBRT. Moreover, given the small number of treatments involved in SBRT delivery, SBRT can easily be combined with chemotherapy, targeted therapies, and immunotherapy with minimal treatment delays. Groups including Schellenberg et al. (2008), Goyal et al. (2012), and Hoyer et al. (2005) have evaluated 25 Gy in one fraction and 45 Gy in three fractions in LAPC (Schellenberg et al. 2011; Goyal et al. 2012; Hoyer et al. 2005). However, the dose and fractionation regimen that best maximizes tumor ablation while maintaining tolerable dose to organs at risk remains under investigation.

Early SBRT studies (Koong et al. 2004; Hoyer et al. 2005) failed to incorporate clear dose constraints or establish methods for image-guided radiation therapy and therefore were associated

Table 1 Stereotactic radiation in locally advanced pancreatic cancer

Study	*N*	Treatment	BED10	Acute/late toxicity (≥Grade 3)	Median local PFS (months)	Median OS (months)
Koong et al. (2004)	15	15 Gy, 20 Gy, or 25 Gy in 1 fraction	37.5–87.5	0%/–	–	11
Hoyer et al. (2005)	22	45 Gy in 3 fractions	112.5	79%/–	4.8	5.7
Schellenberg et al. (2008)	16	Gemcitabine → 25 Gy in 1 fraction → Gemcitabine	87.5	6%/12%	8.4	11.4
Chang et al. (2009)	77	Gemcitabine → 25 Gy in 1 fraction (12% had prior pancreas radiation)	87.5	1%/10%	6.4	11.9
Polistina et al. (2010)	23	Gemcitabine → 30 Gy in 3 fractions	60	0%/0%	7.3	10.6
Rwigema et al. (2012)	71	18–25 Gy in 1 fraction	50.4–87.5	1%/0%	–	10
Schellenberg et al. (2011)	20	Gemcitabine → 25 Gy in 1 fraction → Gemcitabine	87.5	0%/5%	9.2	11.8
Mahadevan et al. (2011)	47	Gemcitabine → 24–36 Gy in 3 fractions → Gemcitabine	43.2–79.2	0%/9%	15	20
Goyal et al. (2012)	19	20–25 Gy in 1 fraction or 24–30 Gy in 3 fractions	43.2–87.5	–/16%	11.4	14.3
Gurka et al. (2013)	11	Gemcitabine + 25 Gy in 5 fractions	37.5	0%/0%	6.8	12.2
Tozzi et al. (2013)	21	45 Gy in 6 fractions	78.8	0%/0%	8	11
Herman et al. (2015a)	49	Gemcitabine + 33 Gy in 5 fractions	54	10%/6%	7.8	13.9

PFS progression free survival, *OS* overall survival

with high rates of acute and late gastrointestinal toxicity (Table 1) (Schellenberg et al. 2011, 2008; Goyal et al. 2012). Toxicities included duodenitis, gastritis, bleeding ulceration, and bowel perforation. These severe toxicities reinforce the need to prioritize gastric, duodenal, and small bowel constraints in close proximity to planning target volumes. Unlike SBRT to the lung and liver, which are surrounded by parallel structures, gastrointestinal organs at risk in pancreatic cancer are organized serially. In light of the gastrointestinal toxicity associated with pancreas SBRT, subsequent trials attempted to minimize toxicity by using modest fractionation, establish clear dose constraints for organs at risk, and incorporate image guidance at the time of treatment delivery. Thus far, studies incorporating 3–5 fractions appear to allow for some degree of normal tissue recovery (Chang et al. 2009). Additionally, the use of induction chemotherapy followed by restaging to ensure the absence of metastases precludes administration of SBRT to patients who are unlikely to benefit (Mahadevan et al. 2011). Polistina et al. treated LAPC patients with sequential gemcitabine followed by 30 Gy in three fractions, with an 82.6% local response rate comprised of stable disease and partial tumor response (Polistina et al. 2010). Additionally, 9% of patients were found to have a complete response, and 8% were downstaged as resectable (Polistina et al. 2010). Furthermore, no grade ≥3 acute or late toxicity was noted. However, median local progression-free survival was 7.3 months and median overall survival from SBRT was 10.3 months. Thus, while the fractionated regimen was tolerable and provided local tumor response and pain control local control efficacy remained short-lived.

The optimal biologically effective dose (BED) for long-term local tumor control remains under investigation. Other recent groups such as

Mahadevan et al. investigated sequential gemcitabine and SBRT to a dose of 24–36 Gy in three fractions (Mahadevan et al. 2011). This regimen's BED closely approximated 25 Gy × 1, and favorable survival outcomes in locally advanced disease were reported, with a median progression-free survival of 15 months and median overall survival of 20 months after chemotherapy and SBRT (Table 1). However, while 0% of patients experienced severe acute toxicity, this radiation dose prescription resulted in 9% of patients with grade ≥3 long-term toxicity. As a result of these data, other groups investigated lower dose and five-fraction regimens. Gurka et al. evaluated gemcitabine and SBRT with 25 Gy in five fractions, with a BED10 of 37.5 Gy (Gurka et al. 2013). Although this regimen was tolerated very well with no grade ≥3 toxicity, local progression-free survival and overall survival from SBRT were only 6.8 months and 12.2 months, respectively. A recent prospective multi-institutional series was published in 2015 by Herman et al. that also examined a five-fraction regimen to a total dose of 33 Gy (Herman et al. 2015a). This phase II trial enrolled 49 patients who received the fractionated regimen coupled with three doses of induction gemcitabine followed by a 1-week break. Patients reported stable quality of life after SBRT from baseline, a significant improvement in pancreatic pain, and had a median overall survival of 13.9 months. Toxicity with this regimen was lesser compared to data from single-fraction trials; however, three (6%) grade 5 toxicities were noted that were related to *Clostridium difficile* infection, sepsis, and GI bleed as a result of direct tumor extension into the duodenum (Herman et al. 2015a).

Overall, there is no consensus with regard to a standard SBRT dose regimen, but the recent literature has peaked interest into further investigation of SBRT as a safe and effective regimen if careful consideration of normal tissue constraints is applied. Local control data are at minimum comparable to standard fractionation, and fractionated SBRT is a well-tolerated and convenient regimen that minimizes systemic treatment delays while improving patient quality of life. The incorporation of more aggressive, contemporary chemotherapy regimens as well as investigation of fractionation and optimal BED to provide tumor control on clinical trials are warranted.

3.3 Hypofractionated Radiotherapy in Locally Advanced Pancreatic Cancer

Conventional fractions of 1.8–2 Gy to 45–50.4 Gy have been ineffective in promoting long-term survival in locally advanced pancreatic cancer, even when using more conformal dose escalation with intensity-modulating radiation therapy (IMRT). Dose escalation to 70–72 Gy was evaluated by Ceha et al. in 2000 and again to 55 Gy by Ben-Josef et al. in 2004 (Ceha et al. 2000; Ben-Josef et al. 2004). Additionally, as discussed previously, trials using ablative BED of SBRT such as 45 Gy in three fractions by Hoyer et al. 2005 to a large field were associated with unacceptable severe treatment toxicity and poor survival outcomes (Hoyer et al. 2005). Thus, currently used SBRT regimens fractionate and prescribe to lower total doses in order to ensure patient safety. While such regimens have reported favorable tumor response rates, there are concerns that the reduced total dose limits the effectiveness of SBRT. Consequently, others have explored extended hypofractionated regimens to permit a total BED that is ablative to the tumor in a manner that allows for additional normal tissue recovery. In 2013, Tozzi et al. published a 45 Gy in six-fraction regimen with a BED10 of 78.8 Gy and Yang et al. have published a dosimetric evaluation of using integrated boost with pancreas SBRT (Tozzi et al. 2013; Yang et al. 2015). Crane et al. at MD Anderson have adopted a 15-fraction regimen to a dose of 67.5 Gy using a simultaneous integrated boost to the hypoxic tumor core in locally advanced pancreatic cancer (Crane 2016). The MD Anderson regimen was developed after extrapolating institutional pancreas and liver BED data, and provides an ablative BED10 of 97.8 Gy (Crane 2016). Institutional data suggest median local progression rates comparable to less advanced disease as well as surgical resection with a local progression-free survival of 15 months and 5-year survival rate of 18% compared to an expected

5-year survival rate of <6% (Crane 2016; Krishnan et al. 2016). Thus, dose escalation through simultaneous integrated boost delivering a definitive BED10 through 15 Gy in hypofractionated doses is a promising approach. However, these patients should be carefully selected because patients treated with this approach require at least a 1 cm separation between the tumor and bowel/stomach.

4 The Role of Adjuvant Radiotherapy in Resectable Disease

4.1 The Controversial Role of Adjuvant Chemoradiation

While there is category I evidence for adjuvant chemotherapy in pancreatic cancer, the role of conventionally fractionated adjuvant radiation remains controversial (Oettle et al. 2013; Evans et al. 2002). Even after curative-intent surgery with negative margins, 45–60% of patients experience local recurrence, with the majority of recurrences developing in close proximity to the celiac axis and superior mesenteric artery (Griffin et al. 1990; Dholakia et al. 2013a). Given this preponderance for local recurrence following surgical resection, several prospective and retrospective studies have examined the role of adjuvant local therapy with radiation. These adjuvant chemoradiation regimens consist of 40–54 Gy in 1.8 Gy fractions, using 3D-CRT or IMRT. While there may be a subset of patients who would benefit from adjuvant CRT, the literature suggests conflicting results with the majority of studies favoring adjuvant chemotherapy alone. As such, the role of adjuvant conventionally fractionated radiation remains unclear and controversial.

4.2 Surgery Alone vs. Adjuvant Chemoradiation

The Gastrointestinal Tumor Study Group (GITSG) (Kalser and Ellenberg 1985) and EORTC 40891 (Klinkenbijl et al. 1999) evaluated adjuvant CRT compared to surgery alone through randomized prospective trials which demonstrated a survival advantage with adjuvant CRT, though this trend was only statistically significant in the landmark GITSG trial (Kalser and Ellenberg 1985). The GITSG trial compared observation following resection to adjuvant CRT consisting of bolus 5-FU-based chemotherapy with a split course of external beam radiation of 40 Gy in 20 fractions followed by maintenance 5-FU (Kalser and Ellenberg 1985). This course of adjuvant CRT resulted in median overall of 20 months vs. 10 months in the control group; however, it was closed prematurely due to poor accrual and large survival differences between the study arms. Subsequently, in 1999, EORTC 40891 randomized patients to surgery alone vs. adjuvant CRT in ampullary and pancreatic cancers. Adjuvant chemotherapy consisted of continuous infusion of 5-FU without maintenance therapy and a similar split-course external beam radiation regimen of 40 Gy in 20 fractions was delivered. While adjuvant therapy demonstrated improved median overall survival (17.1 vs. 12.6 months), and 2-year overall survival (37% vs. 23%), these results were not statistically significant (Klinkenbijl et al. 1999). Another study, Radiation Therapy Oncology Group (RTOG) 9704, primarily explored the role of adjuvant chemotherapy; however, adjuvant radiation was incorporated into both trial arms. Patients were randomized to either gemcitabine or fluorouracil after resection, followed by concurrent 5-FU-based CRT to a radiation dose of 50.4 Gy. While both the adjuvant chemotherapy and radiation regimens differed and results cannot be directly compared to GITSG or EORTC 40891, the median overall survival of 20.6 and 16.4 in the gemcitabine and 5-FU arms, respectively, is similar to the median overall survival of pancreatic cancer patients who underwent resection and adjuvant chemotherapy in the aforementioned trials (Regine et al. 2011). Additionally, large retrospective series from the Johns Hopkins Hospital and Mayo Clinic have demonstrated an improved overall survival with adjuvant 5-FU-based CRT over observation (21.1 vs. 15.5 months) with a propensity score and matched-pair analysis (Herman et al. 2008; Corsini et al. 2008; Hsu et al. 2010).

4.3 Adjuvant Chemotherapy vs. Adjuvant Chemoradiation

Although there is some evidence to suggest that adjuvant therapy with CRT is beneficial compared to surgical resection alone, the bulk of prospective data favor adjuvant chemotherapy alone. Several large retrospective series including a National Cancer Database study and a large, multi-institutional pooled analysis have found a statistically significant benefit in median overall survival associated with adjuvant CRT compared to chemotherapy alone (Morganti et al. 2014; Kooby et al. 2013). Despite these large retrospective series, a meta-analysis of 9 prospective trials published in 2012 and another meta-analysis of 15 prospective trials with various chemotherapy regimens found that adjuvant chemotherapy was associated with improved patient outcomes but there was no statistically significant improvement in overall survival with adjuvant CRT (Ren et al. 2012; Liao et al. 2013). One particularly notable trial is the European Study Group for Pancreatic Cancer (ESPAC)-1, a multi-institution phase III trial with a 2 × 2 randomization of four patient groups: observation, adjuvant 5-FU-based chemotherapy, adjuvant concurrent CRT (using split-course radiation to 40 Gy and 5-FU-based chemotherapy), and adjuvant concurrent CRT followed by an additional six cycles of 5-FU/leucovorin. Survival outcomes favored adjuvant chemotherapy alone (21.6 months); however, the outcomes suggest that the addition of adjuvant radiation therapy to chemotherapy (19.9 months) was associated with improved survival outcomes than with observation alone (13.9 months) (Neoptolemos et al. 2009). Criticisms of this trial include the 2 × 2 randomization scheme, lack of radiation field guidelines or central review of radiation planning, and lack of restaging before adjuvant therapy (Herman et al. 2015b). The ongoing clinical trial RTOG 0848 will further clarify the role of adjuvant radiation therapy following surgical resection (Franke et al. 2015).

Other analyses have explored identification of select patients who may benefit from adjuvant CRT. In a meta-analysis of four randomized controlled trials, Butturini et al. found that chemoradiotherapy in patients with microscopically positive margins (R1) resulted in 28% reduction in the risk of death (HR 0.72, 95% CI 0.47–1.1) (Butturini et al. 2008). This was also demonstrated in another meta-analysis of five randomized controlled adjuvant CRT trials that demonstrated that CRT was more effective in patients with positive resection margins (Stocken et al. 2005). Finally, in a retrospective series from the Johns Hopkins Hospital of adjuvant CRT following resection in patients with distal disease, a subgroup of patients with node-positive disease who received adjuvant CRT correlated with a survival benefit (16.7 vs. 12.1 months) (Redmond et al. 2010). Therefore, there are conflicting data with regard to adjuvant CRT as a standard option, but there may be a subgroup of patients with pathologic features who may benefit.

4.4 Adjuvant Stereotactic Body Radiotherapy in Resectable Disease

Due to the conflicting evidence with regard to the therapeutic benefit of conventionally fractionated radiation, adjuvant chemotherapy alone is used in Europe and controversy surrounding routine adjuvant CRT after negative margins remains in the United States (Tempero 2016). Given the previously described adjuvant CRT data, some institutions reserve adjuvant CRT for patients with an R1 resection and node-positive disease (Tempero 2016). The role of adjuvant SBRT is exploratory, though some postulate that there is utility given that local recurrence is common after surgical resection and that use of SBRT in the margin-positive setting may be beneficial (Goodman 2016). One approach to adjuvant radiation therapy field design encompasses high-risk areas for local recurrence based on mapping of patterns of failure (Dholakia et al. 2013a). In 2012, Rwigema et al.

published a series of 24 patients who were treated with SBRT 20–24 Gy in one fraction adjuvantly after they were found to have close or positive margins (Rwigema et al. 2012). Retroperitoneal margins are the most common site of positive surgical margins, and 87.5% and 62.5% of patients with close and positive margins (respectively) achieved freedom from local progression following SBRT. Moreover, no patients experienced grade 3 or 4 toxicity and patients were able to receive adjuvant chemotherapy shortly afterwards following this short, well-tolerated treatment (Rwigema et al. 2012). However, data for SBRT are limited in the adjuvant setting and adjuvant SBRT remains an ongoing area of investigation.

4.5 Re-irradiation of Locally Recurrent Disease

The use of SBRT as an alternative or adjunct to conventional radiation has also been explored in the locally recurrent setting. The Stanford retrospective SBRT experience published in 2009 included 9 patients with locally recurrent disease who had received a prior course of radiation and 16 patients who received SBRT as a boost to fractionated external beam radiation to 45 Gy (Chang et al. 2009). This treatment was associated with significant toxicities with 25% of (1 of 4) acute toxicities and 33% of (3 of 10) late grade ≥2 toxicities occurring in patients who received external beam irradiation to the pancreas in addition to high-dose SBRT in a single fraction (Chang et al. 2009). Thus, in congruence with the locally advanced pancreatic cancer SBRT literature, single-fraction ablative SBRT regimens are associated with significant toxicities, and other series sought to determine the utility of fractionated regimens. A retrospective series from Georgetown University delivered a boost of SBRT (20–30 Gy in 3–5 fractions) to 28 patients with locally recurrent disease following a median conventional radiation dose of 50.4 Gy (Lominska et al. 2012). Salvage SBRT was well tolerated, though 7% of (2/28) patients experienced late grade 3 toxicity, and was associated with 85.7% freedom from local progression at 6 months (Lominska et al. 2012). Other retrospective series have reported data on fractionated, lower BED SBRT regimens for re-irradiation of locally recurrent disease. Recently, a series reported by Dagoglu et al. report on 30 patients with locally recurrent or progressive disease following conventionally fractionated CRT to 50.4 in 28 fractions (Dagoglu et al. 2016). The SBRT dose of 24–36 Gy in five fractions was associated with a 78% 2-year local control rate, with 10% of patients experiencing grade III acute toxicity and 7% ($n = 2$) with a grade 3 late bowel obstruction (Dagoglu et al. 2016). Moreover, palliative BED prescriptions such as 25 Gy in five fractions have been shown to be well tolerated, associated with 0% acute grade 3 toxicity and a single case (6%) of grade 3 late toxicity in a series of 18 patients reported by the Johns Hopkins Hospital (Wild et al. 2013). Moreover 57% of patients reported palliation of back or abdominal pain, and local progression-free survival at 6 and 12 months was 78% and 62%, respectively (Wild et al. 2013). Therefore, these retrospective series provide evidence that fractionated SBRT may be a useful and tolerable treatment option for patients with local recurrence following prior conventional radiation.

4.6 Neoadjuvant Radiation in Borderline Resectable Disease

Borderline resectable pancreatic cancer (BRPC) is defined as a disease which contacts critical structures such as the superior mesenteric artery, but does not involve these structures to the extent that tumors are technically surgically unresectable (Tempero 2016; Bilimoria et al. 2007). This represents a distinct subset of patients, for which there is currently no standard treatment regimen. Primary management typically involves curative-intent surgery; however, due to the invasion of critical structures, there remains a concern that these patients are at increased risk for positive margins following resection. Currently, there is a lack of category I evidence for the use of neoadjuvant chemotherapy or radiation in borderline resectable patients. At a number of institutions, BRPC patients will undergo

neoadjuvant gemcitabine-based or 5-FU-based chemotherapy (Tempero 2016; Rose et al. 2014). Frequently, neoadjuvant chemotherapy is followed by conventional CRT to a dose of 45–50.4 Gy in 1.8–2 Gy fractions (Katz et al. 2016); however, CRT has only been associated with a 12% RECIST criteria radiographic downstaging in a retrospective series (Katz et al. 2008, 2012; Dholakia et al. 2013b).

A meta-analysis of 111 studies compared neoadjuvant chemotherapy, neoadjuvant radiation, and neoadjuvant CRT in borderline resectable and unresectable pancreatic cancer (Gillen et al. 2010). In this study, while initially resectable patients did not benefit from neoadjuvant therapy, 33% of patients with borderline or unresectable disease were able to undergo surgery and had survival comparable to initially resectable tumor patients following surgery (Gillen et al. 2010). One potential concern for neoadjuvant CRT is that toxicities associated with treatment can potentially delay surgery (Breslin et al. 2001; Spitz et al. 2016). Delivery of fewer fractions of neoadjuvant therapy using hypofractionation has been investigated at MD Anderson, with reported outcomes of 132 patients who received either conventionally fractionated CRT to a dose of 45–50.4 Gy in 1.8 Gy fractions or 30 Gy in 3 Gy fractions (Breslin et al. 2001). The ten-fraction regimen was found to be less toxic although there was no statistically significant difference in survival outcomes. In an institutional review of 160 borderline resectable patients treated with neoadjuvant therapy, 82 patients were considered potentially operable after restaging following neoadjuvant CRT. The majority (80%) of patients were able to undergo surgical resection, with R0 and R1 resection rates of 94% and 6% (respectively), a median survival of 40 months, and a 5-year overall survival rate of 36% (Katz et al. 2008). The authors concluded that this neoadjuvant approach contributed to favorable survival outcomes and allowed for identification of patients who would benefit most from surgery (Katz et al. 2008).

SBRT prescriptions that further increase dose per fraction were also evaluated at Moffitt Cancer Center using gemcitabine-based chemotherapy followed by simultaneous integrated boost in 7–10 Gy in five fractions to the region of tumor-vessel abutment and 25–30 Gy in five fractions to the remainder of the tumor (Chuong et al. 2013). Of the 77 borderline resectable and locally advanced patients, 56% of the BRPC patients underwent surgical resection, with 16.3% of patients achieving a pathologic complete or near-complete response and an overall survival of 16 months. While locally advanced patients were not surgical candidates after neoadjuvant therapy, the authors reported favorable survival at 15 months following neoadjuvant chemotherapy and SBRT. Overall, the treatment regimen was tolerated well without high-grade acute toxicity, but 6% of patients had late grade 3 toxicities including bleeding and anorexia requiring feeding tube placement (Goodman 2016; Chuong et al. 2013). Additionally, data from Johns Hopkins in BRPC and LAPC patients who received neoadjuvant chemotherapy followed by SBRT 25–33 Gy in five fractions also suggest favorable resectability, pathologic outcome, and survival outcomes (Moningi et al. 2015b). Moningi et al. report their institutional experience with 74 LAPC and 14 BRPC patients, 19 (22%) of whom underwent surgery with an 84% margin-negative resection rate and minimal toxicity (Moningi et al. 2015b). Given the response rates, SBRT appears to be an attractive option due to efficacy, tolerability, and short treatment duration and the role of neoadjuvant SBRT in borderline resectable disease is the subject of the currently ongoing Alliance A021501 trial.

5 Stereotactic Body Radiation Treatment Delivery

5.1 Motion Management

The precise and highly conformal nature of SBRT requires effective patient immobilization and target localization in order to accurately target the tumor while allowing for a steep isodose gradient that spares organs at risk. Physiologic organ motion of the pancreas presents a unique challenge due to movement with breathing, gastric filling and emptying, as well as bowel

displacement. CT simulation should be done with both intravenous and oral contrast. 4D imaging which tracks organ motion throughout the respiratory cycle is recommended as well as active breathing control (ABC) or an abdominal belt in order to minimize organ motion due to respiration. During ABC, an inspirational breath-hold technique is used such that treatment is only given during a breath hold to control for respiratory motion, while active respiratory tracking during treatment is also available at some institutions. If a patient is unable to tolerate ABC, an internal target volume (ITV) can be created from a 4D scan or an abdominal compression belt can be used to reduce full excursion of the tumor during the breathing cycle (Goodman 2016). Luminal organ motion is also minimized by encouraging patients to fast before simulation and before each treatment fraction. This allows for reduction in variability of gastric emptying and filling, and also decreases the amount of stomach in close proximity to the planning tumor volume.

5.2 SBRT Planning Volumes

A gross tumor volume (GTV) is defined by CT imaging. Fusion of a magnetic resonance imaging (MRI) scan or positron emission tomography (PET) can also be used to assist with identification of tumor extent. If there is direct tumor invasion of the duodenum and/or stomach on imaging and confirmed on endoscopy, SBRT should only be used if surgery is planned as these patients have a higher risk of bowel toxicity. In these cases, a more protracted regimen (15–30 fractions) is recommended. If ABC is not utilized during simulation, an ITV is created in order to encompass the tumor position when it is maximally displaced by the breathing cycle. An expansion from the GTV or ITV (if no ABC is used) to a planning target volume (PTV) of 1–5 mm is used, based on institutional and medical physics determination of margin required to account for daily setup error with SBRT. At the Johns Hopkins Hospital, the PTV is modified such that it does not overlap with the proximal stomach, duodenum, or bowel volumes more than 2 mm (Fig. 1).

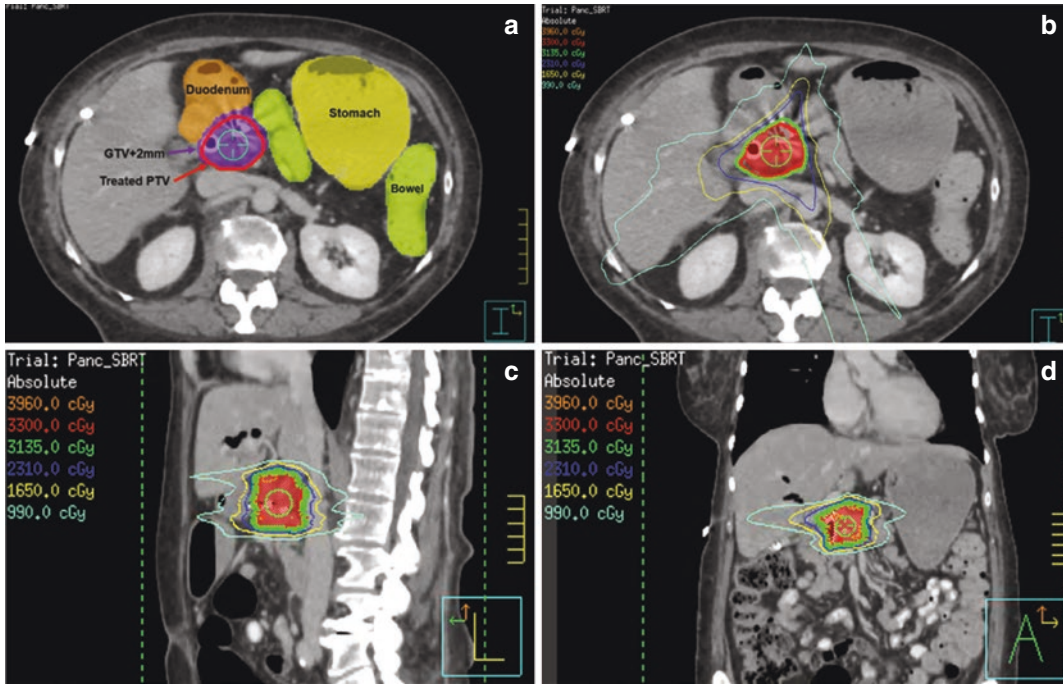

Fig. 1 Pancreas SBRT treatment planning. (**a**) Pancreas SBRT contours of proximal organs at risk and treated PTV. GTV+ 2 mm in *purple* is modified to the PTV used for treatment (*red*) such that there is a 2 mm space between proximal organs at risk and the PTV. (**b–d**) Axial, sagittal, and coronal dose distribution

This modification of PTV volume (modified PTV) is adapted based on the OARs plus a 2 mm (planning organ at risk volume, PRV) expansion. On some clinical trials, simultaneous integrated boost is utilized with 2 or more PTVs in order to boost tumor-vessel interface or the hypoxic tumor core while prescribing a lower dose to the entire PTV or any microscopic areas at risk (Crane 2016).

5.3 Treatment Planning and Dose Constraints

Dose is prescribed to the 60–90% isodose line, to allow for steep dose gradients to minimize dose to the stomach, duodenum, and bowel in close proximity to the PTV. Dose constraints in pancreas SBRT pose a unique challenge, as gastrointestinal organs are organized in serial subunits and proper function is affected by maximum doses. Additionally, the ablative doses of SBRT used in clinical trials exceed the maximum tolerated dose for these structures. The consequences of this were seen in early single-fraction series, which were associated with significant gastrointestinal toxicities. This has been addressed through fractionation, prescribing to lower BED, and modifying the PTV in a way that sacrifices coverage in order to adhere to dose constraints. Although there is currently no standard dose constraint, Murphy et al. published a dosimetric review of SBRT-associated duodenal toxicity in a cohort of 77 patients treated at Stanford (Murphy et al. 2010). They reported dose volume endpoints that were strongly correlated with toxicity. Specifically V15 $\geq$ 9.1 cm^3 and V20 > 3.3 cm^3 were associated with 52% rate of duodenal toxicity compared to V15 < 9.1 cm^3 and V20 < 3.3 being associated with a 11% rate of toxicity (Murphy et al. 2010).

5.4 Tumor Localization

Accurate delivery of SBRT requires confidence in tumor and normal structure location. Challenges to radiation delivery include inter- and intra-fraction tumor and critical organ motion. If SBRT is being utilized in the neoadjuvant or locally advanced setting, use of gold fiducials (ideally 3) placed under endoscopic guidance should be placed adjacent to or within the tumor for kV or MV image guidance. Cone beam CTs are fused with simulation imaging, and used to align patients based on bony anatomy as well as fiducial alignment for accurate target localization and to help evaluate patient setup (Fig. 2). Imaging must be taken immediately prior to delivery, and daily cone beam CTs allow for confirmation that the target volume and organ position are consistent and help to determine if replanning is necessary.

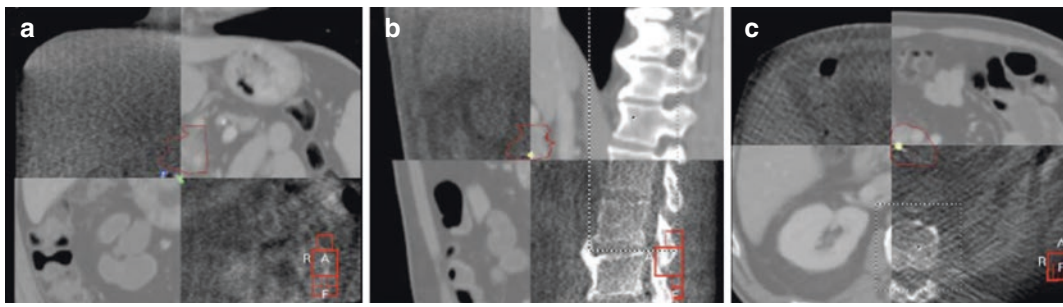

Fig. 2 Patient set-up is verified through daily cone beam CT (*top left*, *bottom right*) which is compared to the patient's reference simulation CT (*top right*, *bottom left*). Patient is aligned to bone and fiducials (*blue*, *green*, and *yellow*) in (**a**) coronal, (**b**) sagittal, and (**c**) axial dimensions and the PTV (*red*) location is also referenced

Conclusion

SBRT in pancreatic cancer is an emerging therapy, which strives to provide local control with curative intent while limiting toxicity and delay in multi-agent chemotherapy administration. Much of the established literature involves locally advanced disease in which the importance of incorporating aggressive systemic therapy and the need to fractionate has been shown to be important in order to provide safe and effective therapy. However, the optimum dose and treatment approach require further investigation to maximize the therapeutic index with a short-course therapy that administers an ablative dose to the tumor while providing a well-tolerated therapy with minimal severe side effects. While the role of adjuvant radiation currently plays an uncertain role in management of disease with negative margins, use of adjuvant SBRT in the setting of positive margins needs further exploration. Moreover, palliatively dosed SBRT (5–6 Gy × 5) has been shown to be both feasible and effective for symptoms and local control in locally recurrent disease, even with re-irradiation. The utility of pancreas SBRT as neoadjuvant therapy for borderline resectable disease and downstaging locally advanced cancer is promising. With continued advancement, the use of pancreas SBRT in the multidisciplinary setting has the potential to provide substantial improvements in long-term survival. Finally, SBRT combinations with novel chemotherapy, targeted therapy, and immunotherapy should be evaluated in well-designed prospective clinical trials.

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