The role of radiotherapy in management of pancreatic cancer

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ABSTRACT   Pancreatic cancer is one of the leading causes of cancer death. The treatment options in pancreatic cancer remain limited. This review provides an overview of the role of radiotherapy (RT) alone or in combination with systemic treatment at different settings of treatment strategy. Neoadjuvant chemoradiotherapy (CRT) may downstage the borderline resectable disease and make resection possible, which could translate to a survival benefit. Although the benefit of adjuvant CRT remains controversial due to inconsistent outcome of randomized trials, in North America it is still a common recommendation of the treatment. For locally advanced pancreatic cancer, the treatment option could either be chemotherapy or chemoradiotherapy. By using advanced radiotherapy modalities, the toxicity of RT could be reduced and RT dose escalation becomes possible to improve locoregional control.

KEY WORDS   pancreatic cancer, chemoradiotherapy, radiotherapy

Introduction

Pancreatic cancer is the 10th most commonly diagnosed cancer and the 4th leading cause of cancer death in the U.S. An estimated 43,140 new cases were diagnosed and 36,800 deaths occurred in the U.S. in 2010. The survival rate for this deadly disease has not improved substantially in nearly the last 40 years even with aggressive treatment. For all stages combined, the 1 and 5-year relative survival rates are 25% and 6%, respectively. For patients diagnosed with local disease, the 5-year survival is only 22% (1). Improving outcomes for patients diagnosed with pancreatic cancer continues to be a formidable challenge.

Surgical resection (pancreaticoduodenectomy) currently provides the best opportunity for long-term survival. However, only 10-20% of patients have resectable disease at the time of diagnosis. The prognosis of patients after complete resection is still poor, with a 3-year disease-specific survival rate of only 27% and a median survival of only15-19 months (2-4). Locally advanced pancreatic cancer (LAPC), in which the tumor encases the celiac axis

or superior mesenteric artery with or without nodal disease but without distant metastases, is by definition unresectable and represents about 25% of the cases at diagnosis. For these patients with LAPC, treatment usually consists of chemotherapy (CT) alone or chemotherapy combined with radiation (CRT), with a resultant median survival only 10-12 months (5-7). Moreover, patients with limited vascular involvement by tumor are considered to have borderline resectable disease and are often treated with non-surgical therapy such as CT alone or CRT.

Patterns of failure data in pancreatic cancer treated with surgical resection alone show that locoregional recurrence is a large component of failure in 50% to 75% of cases (8,9). In addition, hepatic and distant metastases rate is approximately up to 85% to 90% coincident with evidence of locoregional failure. Even in the series that patients received adjuvant treatment after surgery, the locoregional recurrence rate is still as high as 30% - 60% (10,11). Hence, these patterns of failure indicate that current local and systemic treatments are inadequate and there is significant room for improvement.

Traditionally, radiation therapy as local treatment has been utilized as neoadjuvant, adjuvant or definitive treatment with or without systemic therapy. Anywhere from approximately 20% to 80 % of the patients received radiation therapy during the course of their treatment (12). In several other disease sites "models" with high risk of both locoregional and systemic failure, the additional local radiotherapy to systemic chemotherapy has demonstrated improvement of local control and overall

Table 1 Selected studies of neoadjuvant CRT in pancreatic cancer

Trial	No. of patients	Resection rate (%)	Survival (%)	Median Survival in month
Duke University (27)				
CRT	111	55	36 (5 yr. resected)	23
MD Anderson Cancer Center (28, 29)				
Trial 1 CRT (Gem)	86	73	22.7 (5 yr. all) 36 (5 yr. resected)	27 (all)
Trial 2 CT-CRT (Gem)	90	66		17.4 (all) 31.0 (resected) 10.5 (unresected)
Mount Sinai Hospital (30)				
Resectable group	91	100	14 (3 yr.)	14
Unresectable group	68	29.4	21 (3 yr.)*	23.6*
Systematic review and meta-analysis (31)	4392			
Unresetable group		39.1	50.1 (2 yr. resected)	20.5 (resected)
Resectable group		73.6	47.4 (2 yr.)	23.3

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; Gem, gemcitabine; *, P<0.05

survival. Representative examples include gastric cancer and limited stage small cell lung cancer, among others, in which the additional of local radiotherapy reduced the risk of local-regional failure which eventually lead to a decrease in systemic relapses and an improvement in overall survival (13-18). Because of the patterns of recurrence in pancreatic cancer include both locoregional failure in the abdomen and systemic metastasis including the liver; it is logical to consider both local radiotherapy and systemic chemotherapy in the treatment of this cancer. The addition of adjuvant chemoradiation has been reported to decrease local recurrence rates to 20% – 40% (19,20) with some studies even reporting local recurrence rates as low as 10% (21–24). To prospectively evaluate the role of radiotherapy on pancreatic cancer treatment, several randomized trials have been conducted with conflicting results. Hence, the routine utilization of radiation for pancreatic cancer remains controversial.

This review will discuss the role of rationale for using radiation therapy (RT) in the management of pancreatic cancer, review the relevant literature, and discuss current ongoing research and future directions.

Neoadjuvant radiotherapy

A neoadjuvant treatment strategy in pancreatic cancer may offer several theoretical advantages: 1. Pancreatic cancer is more likely a systemic disease with high incidence of distal and local regional failure (10,11). By starting systemic treatment early we may be able to reduce the incidence of distal metastasis and improve survival. 2. Neoadjuvant radiotherapy with or without systemic therapy may potentially downstage the disease and increase likelihood of a complete resection (R0 resection). 3. Radiotherapy can be better tolerated because the normal anatomy of the abdominal region by surgery, such as bowel displacement, which could lead to higher gastrointestinal toxicity, has not been distorted. 4. Neoadjuvant radiotherapy can avoid treating hypoxic tumor tissue caused by surgical disruption of blood supply to tumor cells. In addition, cytokine stimulation after surgery can also potentially adversely affects the efficacy of adjuvant treatment, which can be avoided by neoadjuvant RT (25). 5. Neoadjuvant treatment may also identify those patients with aggressive disease who are likely to develop early metastatic disease, and therefore avoid unnecessary definitive surgical therapy. Given these various rationales for neoadjuvant treatment, several institutions have used this strategy in an effort to improve the survival outcome of patients with pancreatic cancer (Table 1). However, there have been no large randomized controlled trials on the use of neoadjuvant therapy in resectable pancreatic cancer.

The Duke University study investigated neoadjuvant CRT in 96 resectable patients. Patients received daily-fractionated radiotherapy to a total dose of 50.4 Gy concurrent with 5-FU-based chemotherapy. Patients were then re-staged after completion of CRT. Patients were then surgically explored if there was no evidence of metastatic

disease. Subsequently, 70% of patients underwent surgery and 55% had a resection. A R0 resection was achieved in 75% of patients and operative mortality was 3.8%. Overall survival (OS) for resected patients was 28% at 5 years, and a median survival was 23months (26,27).

MD Anderson Cancer Center reported their neoadjuvant treatment results using two different treatment strategies. In their first trial, patients received neoadjuvant gemcitabine and radiotherapy followed by surgery. Radiotherapy was given concurrently with 7 doses of weekly gemcitabine to a total dose of 30 Gy in 10 fractions. Of the 86 patients treated from 2004 to 2006, 64 (73%) underwent resection with an 89% R0 resection rate. The perioperative complication was 9%. The median survival and 5 years OS for all 86 patients were 22.7months and 27%, respectively. Patients, who underwent a resection, did better with a 5 year OS of 36% (28). The second trial was built up on this initial treatment regimen using neoadjuvant combination of chemotherapy prior to of CRT in an attempt to reduce distant metastasis and improve OS (29). Ninety patients were enrolled into this trial. Two cycles of cisplatin and gemcitabine were given before concurrent CRT. Gemcitabine was used for concurrent CRT. Sixty-two patients were deemed radiologically resectable and underwent exploratory surgery. A resection was completed in 52 (66%) patients. Positive margins were found in 1 patient (R1 resection rate of 4%) and nodal disease found in 58% of patients undergoing successful resection. Median follow-up was 29.3 months. The median survival was 17.4 months for all patients and 31 months for those undergoing resection. 27 patients who did not undergo surgical resection had a median survival of 10.5 months. The investigators concluded that the addition of induction cisplatin and gemcitabine chemotherapy prior to neoadjuvant CRT did not improve OS.

In a prospective clinical trial comparing neoadjuvant therapy to up-front surgery conducted at Mount Sinai Hospital in New York City (30), laparotomy and/or CT followed by EUS, angiography or laparoscopy was used to determine potential respectability prior to therapeutic intervention. Sixty-eight patients with locally invasive non-resectable tumors were treated with split-course-chemoradiotherapy (5-FU, streptozotocin and cisplatin) and subsequent surgery if rendered amenable to resection. Thirty of them underwent surgery with downstaging observed in 20 patients. Ninety-one patients with resectable tumors underwent immediate pancreaticoduodenectomy. Sixty-three of them received adjuvant radiotherapy or chemotherapy. The median survival and 3-year OS of all patients receiving preoperative treatment were 23.6 months and 21% compared to 14.0 months and 14% for patients who had initial tumor resection (p = 0.006), respectively.

Recently, a systematic review and meta-analysis of neoadjuvant therapy in 4,394 patients showed that those patients with initial unresectable tumor but who underwent resection after neoadjuvant treatment had comparable survival (median overall survival 20.5 months) to patients with initially resectable tumors (median overall survival 23.3 months) (31). This met-analysis included 111 trials with total of 4,394 patients. Neoadjuvant chemotherapy was given in 96.4% of the studies with the main agents consisting of gemcitabine, 5-FU (and oral analogues), mitomycin C, and platinum compounds. Neoadjuvant radiotherapy was used in 93.7% of the studies with doses ranging from 24 to 63 Gy. Approximately one third of the initial unresectable tumors were resected after neoadjuvant therapy. For patients with resectable tumors, resection and survival rates after neoadjuvant therapy are similar to the ones observed in "up-front" resected tumors that are treated by adjuvant therapy.

Thus, in spite of decades of investigation of neoadjuvant therapy in pancreatic cancer, there is currently no evidence to support its routine use in clinical practice. However, the available data suggest that patients with locally advanced and/or unresectable tumors should be included in neoadjuvant clinical trials and subsequently be evaluated for resection (31).

Adjuvant radiotherapy

The high incidence of locoregional and systemic failure after resection in pancreatic cancer indicates the need for effective adjuvant treatment (8). The role of adjuvant radiotherapy is controversial due to the conflicting results from the randomized controlled trials (Table 2).

The Gastro-intestinal Tumor Study Group (GITSG) conducted first randomized trial in 1980's to evaluate the role of adjuvant CRT in resected pancreatic cancer. Forty-nine patients after R0 resection were randomized to CRT versus observation (32). Radiotherapy was delivered to 40 Gy in 20 fractions with a planned 2-week break after 20 Gy. Bolus fluorouracil (5-FU) was given concurrently and two more cycles after radiotherapy. The treatment arm yielded significantly longer median OS (20 vs. 11 months) and 2-year OS (42% vs. 15%) than the observation arm. Due to this significant improvement in survival, thirty additional patients were treated by the GITSG in a nonrandomized fashion using an identical CRT regimen. The outcome was similar to the treatment arm in the randomized trial (33). Thus, the adjuvant CRT became a standard treatment option for patients with resected pancreatic cancer in North America.

In contrast, the adjuvant chemotherapy is considered

Table 2 Selected studies of randomized and non randomized adjuvant trials in pancreatic cancer

Trial	No. of Patient	Locoregional Failure rate(%)	Survival rate (%)	Median survival in months
Randomized Trials				
GITSG (32)				
No CRT	22	47	15 (5 yr.)	10.9
CRT	21	33	42 (5 yr.)	20.0*
EORTC (34)				
No CRT	57	36	10 (5 yr. pancrease)	12.6 (pancreas)
	103		22 (5 yr. all)	19.0 (all)
CRT	63	36	20 (5 yr. pancreas)	17.1 (pancreas)
	104		25 (5 yr. all)	24.5 (all)
ESPAC1-2x2 (36)				
No CRT	69	62	11 (5 yr.)	16.9
CRT	73		7 (5 yr.)	13.9
CRT + CT	75		29 (5 yr.)	19.9
CT	72		13 (5 yr.)	21.6*
RTOG 97-04 (49)				
CRT	230	28	22 (3 yr.)	16.9
CRT - Gem	221	23	31 (3 yr.)	20.5
Non randomized trials				
Mayo Clinic (48)				
No CRT	180		17 (5 yr.)	19.2
CRT	274		28 (5 yr.)	25.2*
John Hopkins Hospital (47)				
No CRT	345		14.4	15
CRT	271		21.2	20*

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; Gem, gemcitabine; RT, radiation therapy; *, P<0.05

the standard care for patients with resected pancreatic cancer in Europe because the subsequent randomized trials did not confirm the benefit of adjuvant CRT upon survival (34,36,41). In the European Organization of Research and Treatment of Cancer (EORTC) study, 218 patients with pancreatic or periampullary cancer were randomized to CRT versus observation after resection (34). The RT was delivered in the same fashion as in the GITSG trial. Infusion 5-FU was substituted for bolus 5-FU and no maintenance chemotherapy was administered. The median survival in the subset of patients with pancreatic cancer was 17.1 months in the CRT arm versus 12.6 months in the observation arm, a difference that did not reach statistical significance ($P = 0.099$). An update of this trial with longer median follow up of 11.7 years further confirmed the absence of a statistical significant advantage for adjuvant CRT (35). The ESPAC-1 (European Study Group for Pancreatic Cancer) was a randomized trial in a

2 x 2 factorial design. After surgical resection, 289 patients were assigned to observation, CT alone, CRT, or CRT followed by CT (36). In addition, investigators had the option of enrolling patients in 2 similar concurrent trials (one testing CRT vs. observation and one testing CT alone vs. observation), and the data across the 3 trials were pooled for analysis. CRT regimen was similar to those of the GITSG and EORTC trials although the total radiation dose could be 40 or 60 Gy at the discretion of the treating physician. The results showed a beneficial effect of adjuvant CT upon OS, but a deleterious effect of CRT on survival. A more recent analysis included only patients from the 2 x 2 factorial design trial and again showed a benefit for adjuvant chemotherapy (37).

The results of three historical trials evaluating concurrent chemo-radiotherapy (CRT) are confounded by poor design of the trials, sub-optimal compliance of the intended therapy and analysis. The GITSG study

was criticized for slow accrual, small sample size, and suboptimal radiotherapy with a low dose delivered in a split-course fashion. The EORTC trial also employed suboptimal radiotherapy similar to the GITSG study. The omission of maintenance 5-FU, small sample size, high proportion of patients forgoing the assigned therapy, and the inclusion of patients with positive surgical margins without stratification were all considered as study design flaws (38). In addition, it has been argued that statistical significance of this possible benefit is achieved with a one-sided log-rank test, which could have been justified at the time this trial was designed ($P = 0.049$) (39). The ESPAC-1 trial has been strongly critiqued for allowing uncontrolled and previous therapy in a substantial number of patients, introducing a selection bias in the enrollment process and using suboptimal radiotherapy (40). There was also a high rate of non-compliance to the treatment regiments, which questions the validity of any analysis and therefore its conclusions (42).

As mentioned above, all trials employed an outdated radiotherapy regimen using low doses and a split-course delivery; and there was absence of central radiation quality control. All of these factors could have easily adversely impacted the outcomes against the CRT arms. As evidence for this adverse impact, a recent secondary analysis of the Radiation Therapy Oncology Group (RTOG) 97-04 clinical trial showed that failure to adhere to prospectively designated criteria for radiotherapy delivery was associated with inferior survival (43).

The above available randomized trials have generated conflicting results, and so the role of adjuvant CRT remains controversial. In light of this dilemma, several recent studies analyzed survival outcomes in patients who did or did not receive postoperative RT using the Surveillance, Epidemiology, and End Results (SEER) database (44-46). Although each of these studies suffers from possible pitfalls inherent in any retrospective analysis, these analyses have the advantage of long follow up and large patient numbers, which permit subgroup analyses not previously possible with the randomized trials (46). Hazard and colleagues [44] examined the effect of RT in resected pancreatic cancer patients. On multivariate Cox regression analysis, a survival benefit was noted in patients with T3, N1 disease. No survival benefit, however, was seen for tumors limited to the pancreas. A subsequent study by Artinyan and colleagues (45) examined the role of adjuvant RT in a smaller patient population with only node-negative disease. The survival benefit associated with adjuvant RT was observed with hazard ration (HR) of 0.87(95% CI, 0.75–1.00). The latest SEER study by Moody and colleagues (46) included 3252 patients who underwent resection of nonmetastatic disease; the adjuvant RT was associated with increase survival (HR,

0.87; 95% CI, 0.80–0.96). On subgroup analysis, only stage IIB (T1-3N1) patients had a statistically significant benefit associated with RT (HR, 0.70; 95% CI, 0.62–0.79). The age of the patient and stage of disease were identified as independent factors associated with RT use, which means the younger patients with more advanced disease were more likely to receive RT.

Furthermore, two large nonrandomized studies also suggested a survival benefit with adjuvant CRT in pancreatic cancer (Table 2). A prospective study from Johns Hopkins Hospital analyzed 616 pancreatic cancer patients, who underwent surgery. Adjuvant CRT was associated with improved median, 2- and 5-year survivals compared with no CRT (47). Similarly, the Mayo Clinic reported their 3-decade experience of adjuvant therapy in 466 patients, who underwent R0 resection. Adjuvant CRT significantly improved median, 2- and 5-year survival compared with surgery alone. Patients who received CRT had more adverse prognostic factors than that not receiving adjuvant therapy (48). The radiotherapy dose was 50.4Gy in both studies.

Unlike previous discussed trials, the Radiation Therapy Oncology Group (RTOG) 97-04 (49) evaluated the efficacy of gemcitabine in the adjuvant setting compared to 5-Fluorouracil (5-FU). 451 patients were randomized to pre- and post-CRT 5-FU versus pre- and post-CRT gemcitabine after resection of pancreatic cancer. Univariate analysis showed no difference in OS. Pancreatic head tumor patients (n = 388) had a median survival and 5-year OS of 20.5 months and 22% with gemcitabine versus 17.1 months and 18% with 5-FU, respectively. On multivariate analysis, patients on the gemcitabine arm with pancreatic head tumors experienced a trend toward improved OS (P = 0.08). The local recurrence was 28% and the distant relapse rate was 73%. Despite local recurrence being approximately half of that reported in previous adjuvant trials, distant disease relapse still occurred in ≥ 70% of patients. To address the issue of high rate of distant metastasis and further define the role of radiotherapy in adjuvant setting, the current EORTC/U.S. Intergroup RTOG 0848 phase III adjuvant trial evaluates the impact of targeted therapy Erlotinib and CRT on OS after completion of a full course of gemcitabine. The impact of adjuvant CRT vs. CT on outcome of pancreatic cancer is another end point of this study

Definitive radiotherapy in locally advanced pancreatic cancer

Thirty percent of patients present as locally advanced pancreatic cancer (LAPC) at time of diagnosis (1). The definition of LAPC is unresectable disease in the absence of distant metastases. But in practice, borderline

Table 3 Selected studies of randomized trails of definitive CRT in pancreatic cancer

Trial	No. of patient	Survival rate (%)	Median Survival in month
GITSG (1981) (53)			
40-Gy CRT (5-FU)	83	40 (1 yr.)	10
60-Gy CRT (5-FU)	86	40 (1 yr.)	10
60-Gy RT	25	10 (1 yr.)	6*
ECOG (1985) (54)			
40-Gy CRT (5-FU)	34	28 (1 yr.)	8.3
CT (5-FU)	37	28 (1 yr.)	8.2
GITSG (1988) (55)			
40-Gy CRT (5-FU - SMF)	24	41 (1 yr.)	10
CT (SMF)	24	19 (1 yr.)	8*
FFCD/SFRO (2008) (56)			
60-Gy CRT (5-FU +CDDP – Gem)	59	32 (1 yr.)	8.6
CT (Gem)	60	53 (1 yr.)	13*
ECOG 4201 (2008) (5)			
50.4 Gy CRT (Gem)	34	45	11
CT (Gem)	35	30	9.2*

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; RT, radiation therapy; 5-FU, 5-fluorouracil; Gem, gemcitabine; CDDP, cisplatin; SMF, streptozocin, mitomycin, 5-FU.

*. P<0.05.

respectable tumor should be regarded as LAPC because of the high likelihood of achieving an incomplete (R1 or R2) resection. Patients with LAPC are potentially curable if a R0 resection (R0) can be performed after downstaging of the tumor, therefore it should be treated with the intention of delivering curative therapy (31). Quite often, LAPC is treated with chemotherapy, which improves quality of life and survival when compared with best supportive care (50). The additional local treatment with RT may slow the progression of local disease and offer palliation and /or prevention of of symptoms, such as pain, biliary obstruction, bleeding, or bowel obstruction. When chemotherapy is combined with RT, long-term survival has been reported (51). However, the role of radiotherapy in LAPC still remains undefined.

The advantage of CRT over best supportive care was studied in a small prospectively randomized trial (52). 16 patients received CRT and 15 had supportive care. The RT dose was 50.4 Gy (ranged from 25.2 to 60 Gy) and CT was continues infusion 5-FU at 200 mg/m2/d. The median survival was 13.2 months for CRT group vs. 6.4 months for support care. The study demonstrated significant improvement of OS and quality of life in the patients received CRT.

Early GITSG randomized trial compared combined CRT (using RT doses of 40 Gy and 60 Gy with 5-FU)

followed by additional CT vs 60 Gy RT alone (53). Combined CRT was significantly superior to radiotherapy alone, with mean OS times of 10.4 vs. 6.3 months. Higher dose (60 Gy) of radiotherapy did not improve OS compared to 40 Gy, although this may have been also a function of the old delivery technique (2-D) of RT. This study established general consensus that radiotherapy should be given concurrently with chemotherapy in patients with LAPC. Several subsequent randomized trials have compared chemotherapy alone to CRT in LAPC, including 2 ECOG trials (1989, 2008), 1 GITSG trial (1988), and 1 trial by the Fondation Francophone de Cancerologie Digestive and Societe Francaise de Radiotherapie Oncologique (FFCD/ SFRO) (Table 3) (54,5,55,56). Two studies (ECOG 1985 and FFCD/SFRO) showed no survival benefit to CRT. It should be noted that radiotherapy delivery in ECOG 1985 trial was sub-optimal with split-course RT technique; and FFCD/SFRO trial used unusually high dose radiotherapy and non-standard chemotherapy regimen (5-FU and cisplatin) in this setting with increasing toxicity. The GITSG (1988) study and the ECOG 4021 demonstrated survival benefit to CRT. The split-course of radiotherapy and more toxic chemotherapy regimen (streptozotocin, mitomycin, and 5-FU) used in GITSG (1980) could have adversely affected the study outcome. The ECOG4201 is only study using modern radiotherapy techniques (3-D
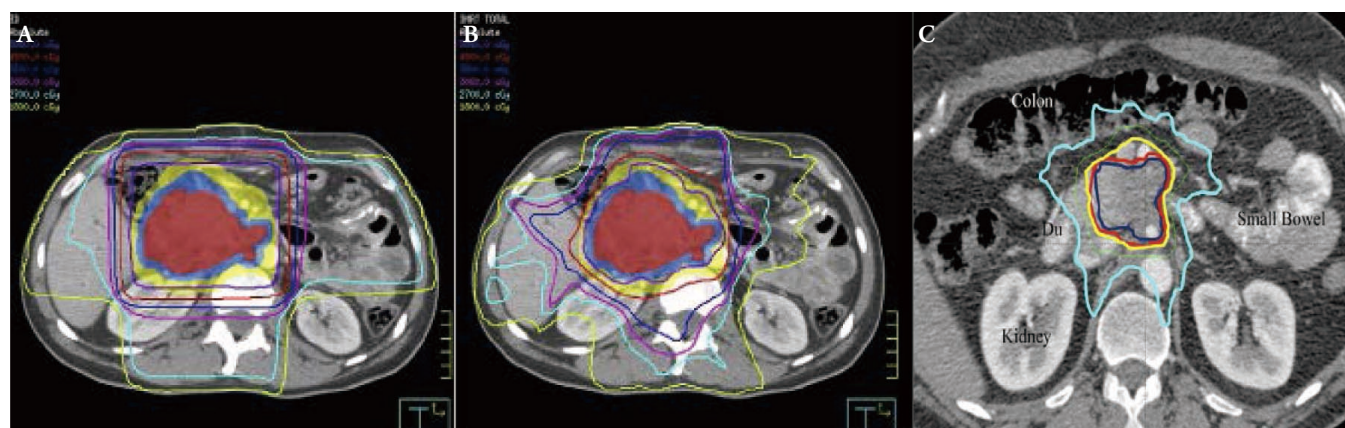
Figure 1 Illustration of isodose plans from 3-D (A), IMRT (B) and SBRT (C).

conformal radiotherapy) and more effective chemotherapy gemcitabine (5). Thirty-eight patients were treated with gemcitabine alone and 36 with gemcitabine-based CRT. The dose of radiation was 50.4 Gy. The results showed a small but significant 2-month improvement in median survival with the addition of RT (11.0 months vs. 9.2 months, P<0.05). The median time to progression was also improved with RT. Although the trial accrued only 74 out of 316 patients as study planned, the results suggest that there may be a role for RT in patients with locally advanced disease, in conjunction with gemcitabine chemotherapy.

Advances in radiotherapy

In majority of the trials published before the early 1990s, conventional RT with larger fields of radiation encompassing the pancreas or pancreatic bed and regional nodes with margin were used. The use of this large volume of radiation fields contributed to high incidence of GI toxicity, especially when concurrent chemotherapy was employed. Three-dimensional conformal radiotherapy (3-DRT), which uses acquired CT images to allow delineation of target volumes and precise localization of normal structures, provides optimum coverage of the target and maximal sparing of surrounding normal critical organs and tissues. Intensity modulation radiation therapy (IMRT) is a more recent advance in the delivery of RT. It generates more conformal coverage of RT on target and maximizes the sparing normal tissue than 3-DRT. University of Maryland treated 46 patients with adjuvant CRT using IMRT (57). The RT field included elective nodal areas. All patients received CRT based on 5-FU in a schema similar to RTOG 97-04. Rates of acute gastrointestinal (GI) toxicity from this study were compared with those from RTOG 97-04, where all patients were treated with 3-DRT (Figure 1A and

B). The overall incidence of Grade 3–4 acute GI toxicity was significant lower in patients receiving IMRT-based CRT compared with patients who had 3-DRT. With IMRT, it is possible to deliver doses of 45 to 50 Gy to the typically larger RT fields while escalating the dose to the tumor bed to 54 to 60 Gy (58). Such dose escalation may be necessary for patients with high risk of local recurrence. The higher dose of radiation integrated with newer chemotherapeutic and targeted agents, may be needed to improve both local control as well as overall outcome in this subset of patients.

Several other methods for precise targeting and dose escalation have been studied, including stereotactic body radiation therapy (SBRT). SBRT delivers 1 to 5 ablative doses of radiation to small area only including gross disease with tight margin, as opposed to conventional fractionation of 25 to 28 lower-dose fractions to a large field over normal tissue to cover microscopic extension of disease and regional lymph nodes. The studies using SBRT have demonstrated high rate of feasibility with high rate of local control, but with increase toxicity (Figure 1C) (59-62). In a phase II study, SBRT was give to total dose of 30 Gy in 3 fractions to unresectable pancreatic carcinoma [62]. The local control rate was 57%; however, small-bowel toxicity was high (18%), consisting of severe GI mucositis/ ulceration, alone with a 4.5% perforation rate. In a trial conducted at Stanford University, single dose of 25 Gy SBRT was given to a small radiation field. An 84% local control rate at 12 months was reported with 4% grade 2 late toxicity and 9% grade 3 or 4 late GI toxicity (60). Mahadevan et al. reported their experience on SBRT using 3 fractions to total dose of 24 -36 Gy (61). After SBRT, patients received gemcitabine for 6 months or until tolerance or disease progression. On 36 patients with median follow up 24 months, the local control rate was 78% and the median survival was 14.3 months. Seventy-eight percent of patients developed distant

metastasis. There were 25% grade II and 14% grade III GI toxicity. The other application of SBRT in LAPC is to boost primary tumor site after conventional radiotherapy with or without chemotherapy. The Stanford University group (62) enrolled 19 patients onto a prospective study to evaluate this boost concept. 25 Gy single fraction SBRT was delivered to primary tumor site after 45Gy of conventional radiotherapy delivered in 5 weeks. The local control rate was 94% with 12.5% incidence of late duodenal ulcers. Although the local control rate have been impressive, given the higher rates of GI toxicities and that improved local control has not translated into a survival benefit in these trials, caution should be exercised in using this type of approach.

RT field size is a current topic of interest and research, especially given the increasing interest in dose escalation and more intensity of systemic treatment. Historically, radiation fields have been large, encompassing the pancreas or pancreatic bed with a 2- to 3-cm margin and including lymph node regions, which may be harboring microscopic disease. Growing evidence from other tumor models such as non-small cells lung cancer suggests that small-involved field radiation may be reasonable without compromising local regional control and overall survival (63,64). In a phase I trial of full-dose concurrent gemcitabine and small-involved field radiotherapy for LAPC, there was only 1 of 23 patients developed regional nodal recurrence. This trial showed that smaller RT field size might be reasonable (63). In another study using involved field radiation concurrently with full dose of capecitabine 500-600 mg/m2 twice daily, the local and locoregional progression were 14% and10%, respectively. 14 % patients presented with local and systemic disease. There was only one patient who had grade III GI toxicity (64). Although these data are encouraging, the further investigation is still necessary to confirm the use of involved small field of radiation.

Conclusion

The treatment of pancreatic cancer remains challenging. The dismal outcome after various therapeutic strategies highlights the need for continued study of optimizing current treatment and incorporating novel agents into existing regimens. The use of chemotherapy and particularly radiotherapy are controversial because of difficulties interpreting the available randomized data. In neoadjuvant setting, there is no evidence to support routine use of neoadjuvant CRT for resectable disease. However, some patients with borderline resectable pancreatic cancer may benefit from neoadjuvant CRT if the resection can be performed. The assessment of resectability after neoadjuvant CRT is critical to determining the need for surgery, which

can have a significant impact on patient survival. With advanced diagnostic images such as CT scan, MRI, PET scan EUS, even minimal invasive procedure of laparoscopy, it is possible to select out such patients, who can be benefit from R0 resection. Newer techniques of delivering RT such as IMRT and SBRT offer the opportunity to improve the efficacy of neoadjuvant treatment due to its better tolerance with chemotherapy and the potential for RT dose escalation. In the adjuvant setting, CRT is still considered as a standard treatment option in North America. But if an R0 resection can be achieved, only chemotherapy can be recommended. Currently, a reasonable therapeutic strategy in the adjuvant and the definitive settings includes an initial 2 to 4 months of gemcitabine-based chemotherapy, followed by restaging and delivery of 5-FU–based CRT, or gemcitabine-based CRT using 3-DRT or IMRT to involved fields. Further investigations are needed to define more clearly the optimal timing of radiotherapy, dose, field size, and technique. In addition, the employment of more potent systemic agents, including those with radiosensitizing properties may further enhance the efficacy of RT (65). Several phase I/II trials are exploring the efficacy of targeted agents and alternative chemotherapeutic agents (66). ACOSOG Z05031, a phase II trial using cisplatin, 5-FU and α-interferon, has shown promising 2-year OS rate of 55% of and a median survival of 27.1 months (67). Currently, on going RTOG 0848 phase III adjuvant trial is evaluating impact of Erlotinib with CRT on survival in pancreatic cancer.

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