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Adjuvant therapy for pancreas cancer in an era of value based cancer care

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ABSTRACT

In resected pancreas cancer, adjuvant therapy improves outcomes and is considered the standard of care for patients who recover sufficiently post operatively. Chemotherapy or combined chemotherapy and radiation therapy (chemoradiation; CRT) are strategies used in the adjuvant setting. However, there is a lack of evidence to suggest whether the addition of RT to chemotherapy translates to an improvement in clinical outcomes. This is true even when accounting for the subset of patients with a higher risk for recurrence, such as those with R1 and lymph node positive disease. When considering the direct and indirect costs, impact on quality of life and questionable added clinical benefit, the true "net health benefit" from added RT to chemotherapy becomes more uncertain. Future directions, including the utilization of modern RT, integration of novel therapies, and intensifying chemotherapy regimens may improve outcomes in resected pancreas cancer.

Introduction

Pancreas cancer remains the fourth leading cause of cancer deaths in the United States with a dismal prognosis and a 5-year overall survival of <5% across all stages [1]. In 2014, there were approximately 46,420 new cases of pancreatic cancer with only 9% with localized disease [2]. Patients with localized disease that is deemed resectable will undergo a pancreaticoduodenectomy (Whipple procedure) or a distal pancreatectomy with the intent to achieve a complete (R0) resection [3,4]. Despite a curative intent, most patients will eventually succumb to recurrent disease [5]. Adjuvant therapy improves relapse free and overall survival following resection and the administration of adjuvant treatment is considered the standard of care for patients who recover sufficiently within 4–12 weeks post operatively [6]. While the role of chemotherapy (CT) has been established in randomized trials, there is no consensus on the role of combined chemotherapy and radiation (chemoradiation; CRT) due to inconsistent results from trials. Herein, we provide an overview on the role of adjuvant therapy in pancreatic cancer, a cost analysis based on the various modalities and an assessment of future directions integrating novel therapeutic strategies.

Adjuvant therapy following resection

The role of adjuvant chemotherapy in resected pancreatic cancer

Numerous studies investigating the use of adjuvant chemotherapy have shown a significant improvement in clinical outcomes in comparison to observation. CONKO-001, which investigated the use of adjuvant gemcitabine versus observation, showed a significant improvement in disease-free survival of 13.4 months in patients who received adjuvant chemotherapy vs. 6.9 months in the observation group [7]. This finding was consistent across all subgroups, including patients with node-positive disease and microscopically positive margin (R1) resections. Updated results from this trial revealed a significant overall survival benefit for adjuvant gemcitabine, with a median overall survival of 22.8 months in the gemcitabine group vs. 20.2 months (HR 0.76, $p = 0.01$) in the observation group [8]. Results from a smaller phase III Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer trial resulted in similar findings to CONKO-001 [9]. Another large study, ESPAC-3 compared the benefits of adjuvant gemcitabine, bolus 5-fluorouracil and leucovorin (5-FU/LV) or observation in resected pancreatic adenocarcinoma (Table 1) [10]. The observation arm was removed from the design following the results of ESPAC-1 [11], which demonstrated that chemotherapy (5-FU/LV) was superior to observation and CRT. There was a comparable overall therapeutic benefit for the 2 chemotherapy arms (23.0 vs

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Table 1
Summary of randomized post-operative adjuvant therapy trials in pancreas cancer.

Study	No. of patients	Treatment	% R1	% LN +	% Locoregional recurrence	Median OS	P Value	Median DFS	P Value	% G3–4 toxicity
ESPAC-1[a] [11]	289	5-FU	19	53	35	20.1	0.009	15.2	0.04	4
		CRT	19	50		15.9		10.7		6
ESPAC-3[b] [10]	1149	5-FU	14	62	NR	23	0.39	14.1	0.53	14
		G	15	60	NR	23.6		14.3		7.5
RTOG 9704[c,^] [14]	451	5-FU/CRT	33	65	30	16.9	0.15	11.1	NR	62
		G/CRT	35	68	31	18.8		11.2		79
CONKO-001[d,*] [7,8]	354	G	19	71	34	22.8	0.01	13.4	<0.001	5
		Observation	15	73	41	20.2		6.7		1
JSAP-02[e,*] [9]	378	G	19	67	23	22.3	<0.001	11.4	0.01	26
		Observation	8	70	32	18.4		5		NR
GITSG[f] [12]	43	CRT	19	29	15	20	0.03	11	0.01	7
		Observation	24	27	15	11		9		
CONKO-005[g]	436	G	0	66	NR	26.5	0.406	11.6	0.291	45.4
		G + E	0	64	NR	24.6		11.6		63

G-gemcitabine, E-erlotinib, 5-FU (5-fluorouracil), CRT-chemoradiation, CT-chemotherapy.
^ Findings in RTOG 9704 presented local recurrence and lymph recurrences separately, which we combined for conformity.
* In addition to adenocarcinoma, they included other histology.
[a] 5-FU (425 mg/m^2) + LV (20 mg/m^2 bolus) × 5 days (every 28 days × 6 courses). 20 Gy in 10 daily fx with IV bolus 5-FU (500 mg/m^2 days 1–3 of RT and again after planned 2 week break).
[b] (143) 5-FU-LV (20 mg/m^2 bolus), followed by 425 mg/m^2 5-FU days 1–5 every 28 days × 6 courses. (141) Gemcitabine 1 gm/m^2 IV once a week for 3 of every 4 weeks × 6 courses.
[c] 5-FU (continuous infusion 250 mg/m^2) or Gemcitabine (1 gm/m^2 once a week) for 3 weeks prior to CRT. CRT continuous infusion of 5-FU (250 mg/m2 per day) with 50.4 Gy (in 28 fx).
[d] Gemcitabine 1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses.
[e] Gemcitabine (1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses).
[f] CRT-5-FU (500 mg/m^2 IV bolus daily × 3d) with 2D RT (split course radiation, 40 Gy (20 Gy × 2 separated by interval of 2 weeks)), followed by 5-FU (500 mg/m^2 IV bolus once weekly × 2 years or until recurrence.
[g] Gemcitabine (1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses). Erlotinib (100 mg/d p.o. daily) × 6 courses.

23.6 months in the 5-FU/LV and gemcitabine arms) with a more favorable toxicity profile associated with gemcitabine (Table 1). Based on these studies, there appears to be a clear clinical benefit for patients with resected pancreatic adenocarcinoma receiving adjuvant chemotherapy regardless of nodal and resection status.

The role of adjuvant chemoradiation therapy in resected pancreatic cancer

Earlier randomized clinical trials investigating the role of combined chemotherapy and radiation (CRT) have been largely underpowered with flawed designs and mixed results. Nonetheless, CRT had been recommended as a treatment option in the adjuvant setting. The historical precedent for adjuvant chemoradiotherapy stems from the results of the Gastrointestinal Tumor Study Group (GITSG) 9173 trial published in 1987, which demonstrated a 9-month survival benefit for adjuvant fluorouracil (5-FU) based chemoradiation over observation in resected pancreatic cancers (20 months in the chemoradiation group versus 11 months in the observation arm) [12]. The study was underpowered with 43 patients included in the analysis. An archaic 2D radiation technique was utilized, where patients received two 20 Gy courses (total 40 Gy) separated by 2 weeks, with large treatment radiation fields (covered residual pancreas, pancreatic bed, and at-risk lymph node regions). Subsequent trials attempting to confirm the benefit of adjuvant chemoradiation were not able to reproduce similar findings (Table 1). In 1999, the EORTC study, which compared adjuvant chemoradiotherapy to observation in pancreas cancer, showed a non-statistically significant trend towards a survival benefit [13]. Similarly to GITSG, a split course of radiation (2 × 20 Gy separated by two weeks, total 40 Gy) was administered to patients, utilizing 3D radiation technique with tissue limits to the liver, kidneys and spine. A subset analysis did suggest a trend towards survival benefit in patients with pancreatic head tumors only, with a 2 year overall survival of 34% versus 26% in the observation group ($p = 0.099$) [13].

More recently, published in 2008, RTOG 9704, a phase III randomized controlled trial, investigated the role of adjuvant concurrent 5-fluorouracil (5-FU) and radiation, sandwiched between either 5-fluorouracil (5-FU) or gemcitabine. This was the first modern radiation therapy randomized phase III trial, where standardized guidelines were given in regards to radiation fields, dosing and targets. RT was conducted by 3D technique (no IMRT), administering 45 Gy with 1.8 Gy fractions to all targets, followed by a boost of 5.4 Gy (over 3 fractions) to the tumor bed, for a total of 50.4 Gy. The results of this study showed no major differences in patient outcomes between gemcitabine and 5-FU in the adjuvant setting, except in patients with tumors in the head of the pancreas where gemcitabine seemed to be of further benefit (20.5 versus 16.9 months). Despite the use of modern radiation techniques and quality control measures, the locoregional recurrence rate remained relatively high in both treatment arms (Table 1) [14]. Additionally, grade 3 or 4 toxicities were high in both treatment arms, which were 62 and 79 percent in the 5-FU and gemcitabine arm. The design of RTOG 9704 was to compare two different regimens in the adjuvant setting, but failed to address the potential added role for radiation therapy in resected pancreatic cancer. Therefore findings from this study did not address the role of adjuvant chemo-radiation therapy in this disease.

Chemotherapy (CT) versus chemo-radiation therapy (CRT): What should the standard be?

The role of adjuvant CT is well established in patients with resected pancreas cancer. However, there is a noticeable paucity of studies that help us understand the added role of radiation (as in CRT) to CT in resected pancreas cancer. One such study is ESPAC-1, a phase III randomized control trial that attempted to address the role of radiation therapy in resected pancreatic cancer by comparing the overall benefits of CRT vs. CT. The trial used a two-by-two factorial design in which patients were randomized to receive CRT or CT, observation, or both treatments. RT was