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Meta-analyses of treatment standards for pancreatic cancer (Review)

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Abstract. Pancreatic cancer is the most lethal common cancer with an estimated 5-year survival rate of 6-7% (across all stages). The only potential curative therapy is surgical resection in those with localized disease. Adjuvant (postoperative) therapy confers a survival advantage over postoperative observation alone. Neoadjuvant (preoperative) therapy offers the potential to downstage initially unresectable tumors for resection, sterilize resection margins and decrease locoregional recurrence, and identify a subset of patients with aggressive disease for whom surgery will not be beneficial. Induction chemotherapy followed by consolidation chemoradiation is another recommended approach in those with locally advanced disease. For those who cannot be downstaged, cannot tolerate surgery, or were diagnosed with metastatic disease, treatment remains palliative with chemotherapy being a critical component of this approach. Recently, intensive combination chemotherapy has been shown to improve survival rates in comparison to gemcitabine alone in advanced disease. The past few decades have afforded an accumulation of high-level evidence regarding neoadjuvant, adjuvant and palliative therapies in pancreatic cancer. There are numerous reviews discussing recent retrospective studies, prospective studies and randomized controlled trials in each of these areas. However, reviews of optimal and recommended treatment strategies across all stages of pancreatic cancer that focus on the highest levels of hierarchical evidence, such as meta-analyses, are limited. The discussion of novel therapeutics is beyond the scope of this review. However, an extensive and the most current collection of meta-analyses of first-line systemic and locoregional treatment options for all stages of pancreatic cancer to date has been accumulated.

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1. Introduction

Epidemiology. Although pancreatic cancer represents only 2.8% of all new cancer cases in the US, it is the fourth leading cause of cancer fatality in men and women (1). Of the estimated 48,960 new cases of pancreatic cancer in the U.S. in 2015, an estimated 40,560 are expected to succumb to the disease (2). Worldwide, pancreatic cancer is the eighth and ninth leading cause of cancer fatality in men and women, respectively, with an incidence of 2-8 cases per 100,000 people and a greater predilection in men and developed countries (3). Accounting for 85% of all types of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC) is often synonymous with pancreatic cancer and tends to occur more in the elderly (median age of 71 years at diagnosis) and at an advanced stage (<20% present with localized and resectable disease) (4,5). In total, 60-70 and 20-25% of pancreatic cancers occur in the head and body/tail of the pancreas, respectively, with symptoms and signs related to the location (5).

2. Localized and resectable pancreatic cancer (stage I or II)

Surgery. The only potential curative therapy for pancreatic cancer remains surgical resection in the 15-20% of cases meeting criteria for localized and resectable disease (stage I or II) following diagnosis (4-6). In particular, pancreaticoduodenectomy (the Whipple procedure) with standard lymphadenectomy and distal pancreatectomy with splenectomy are the surgeries of choice for cancers of the head/neck and body/tail, respectively (4-6). The median survival is 17-27 months in those with resected pancreatic cancer with 5-year survival rates of 15-20% (7,8). However, of the 15-20% of candidates who undergo surgical resection, 66-92%

experience disease recurrence within 2 years of resection with local recurrence rates of 35-60% and systemic recurrence rates as high as 80-90% (8,9).

Adjuvant therapy. Adjuvant (postoperative) therapy in the form of chemotherapy or chemoradiotherapy has been shown to confer a survival advantage compared to postoperative observation alone (10-18). Meta-analyses of trials involving gemcitabine or 5-fluorouracil (5-FU)-based regimens show that adjuvant chemotherapy, when compared to postoperative observation alone, significantly improves survival [as much as 7 months in increased median overall survival (OS)] in those with negative-margin (R0) resections, although this effect is less pronounced in those with microscopically positive-margin (R1) resections (19-24). Following adjustment for confounding factors, adjuvant therapy with gemcitabine or 5-FU again provided an OS benefit over observation alone with hazard ratios (HRs) of 0.59 [95% confidence interval (CI), 0.41-0.83] and 0.65 (95% CI, 0.49-0.84), respectively (22). Significant differences in survival were not observed when comparing adjuvant gemcitabine and 5-FU arms (22). Results are more conflicting for adjuvant chemoradiotherapy as a majority of meta-analyses reveal that chemoradiation does not significantly confer a survival advantage over upfront surgery alone or those not receiving adjuvant chemoradiation, although it may provide a small survival benefit in those with R1 resections (Table I) (19,21,22,24-26). One meta-analysis was the first to use Bayesian analysis to demonstrate that adjuvant chemoradiation ± chemotherapy incurs greater toxicity yet does not confer a survival advantage compared to adjuvant gemcitabine or 5-FU alone (22).

Although the role of radiotherapy as a component of adjuvant therapy remains controversial, 6 weeks of 5-FU-based chemoradiation preceded, followed by maintenance chemotherapy remains an acceptable alternative form of adjuvant therapy (7,8,18,27,28). As thought previously, radiotherapy may further benefit a subset of patients undergoing R1 resections or at increased risk of locoregional recurrence (7,8). Currently, 6 months of adjuvant chemotherapy with gemcitabine or 5-FU remains the standard for adjuvant therapy in those with resected pancreatic cancer (8,13,29,30). Current trends in the treatment of resected pancreatic cancer in the US reflect on the recent publications of landmark trials as the use of adjuvant chemotherapy alone increased <250%, while the use of adjuvant chemoradiation decreased as much as 42%, although chemoradiotherapy remains in slightly greater use compared to chemotherapy for adjuvant therapy (31). Furthermore, although early initiation of postoperative chemotherapy was once emphasized, it has now been demonstrated that completion of all 6 cycles of adjuvant therapy, rather than time to initiation of therapy, is critical to the survival outcome, as no differences in outcome were observed in those in which adjuvant chemotherapy was delayed <12 weeks (32,33). Of note, a recent phase III trial failed to show significant differences in survival between adjuvant 5-FU with folinic acid and adjuvant chemoradiation including 5-FU, cisplatin, and interferon α-2b, while a Japan-based phase III trial showed that adjuvant S-1, an oral fluoropyrimidine, was superior to adjuvant gemcitabine, although metabolic differences between Asian and Caucasian ethnicities limit its application in the West for resected pancreatic cancer (34-36).

Neoadjuvant therapy. Evidence suggests that neoadjuvant (preoperative) therapy in localized pancreatic cancer (LPC) may improve rates of R0 resections, decrease locoregional recurrence, and identify a subset of patients (on restaging) with aggressive disease for whom surgery will not provide a survival benefit (4,7,8,37). Although ~25% of those who undergo upfront surgery for localized disease are unable to complete adjuvant therapy, neoadjuvant therapy ensures that almost all can receive some form of treatment, although it carries the risk of disease progression in delaying potentially curative resection (7,38,39). Neoadjuvant therapy with chemotherapy alone or predominantly 5-FU or gemcitabine-based chemoradiation ± preceding chemotherapy followed by resection offers survival rates that compare favorably to those observed with resection followed by adjuvant therapy (Table II) (37-41). Despite higher rates of perioperative mortality, neoadjuvant therapy followed by resection demonstrates superior cost-effectiveness with postoperative morbidity and mortality rates that are comparable to those observed with upfront surgery for LPC (42,43). Neoadjuvant therapy represents a rational alternative to a 'surgery-first' approach to LPC; however, is considered investigational due to the lack of complete and definitive data from phase III trials (8,44). There are ongoing phase III trials involving neoadjuvant therapy followed by surgery versus upfront surgery with adjuvant therapy and neoadjuvant therapy with adjuvant therapy versus adjuvant therapy alone (https://clinicaltrials.gov/).

3. Borderline resectable and locally advanced pancreatic cancer (stage III)

Neoadjuvant therapy. Approximately 30% of patients diagnosed with pancreatic cancer have locally advanced and unresectable disease (stage III) with a median survival of 8-12 months and 5-year survival rate of ~6% (4,7,45). Neoadjuvant therapy can potentially downstage tumors to increase R0 resection rates in a subset of patients with 'borderline resectable' disease, as well as downstage those with locally advanced disease for possible resection (7,8,45,46). In those with initially unresectable disease (borderline resectable/locally advanced), neoadjuvant therapy with chemotherapy alone or, more commonly, 5-FU or gemcitabine-based chemoradiation ± preceding induction chemotherapy ± sequential chemotherapy has produced, for the most part, resectability rates of 30-40% (although with higher perioperative morbidity and mortality rates compared to initially resectable tumor patients) and, when followed by surgery, survival times within the range of those observed with upfront surgery followed by adjuvant therapy for initially resectable disease (Table II) (38-40,47-49).

In borderline resectable disease, a majority of retrospective and prospective studies using variations of gemcitabine-based chemotherapy alone or gemcitabine, capecitabine, or 5-FU-based chemoradiation ± induction chemotherapy, have demonstrated resectability rates with high probability for R0 resections and survival times comparable to those in the meta-analyses described previously (Table II) (50,51). Some, however, have argued that radiographic downstaging following neoadjuvant therapy is uncommon in borderline resectable disease, despite high rates of R0 resections achieved in patients without evidence of radiographic response. Therefore, it has

Table I. Meta-analyses of adjuvant therapy in localized pancreatic cancer.

Study	Included trials	Analytic arm(s)	Main end point(s)	Findings	(Refs.)
Morganti *et al* 2014	Multicenter pooled analysis (955 patients)	A: CRT vs. OBS B: CRT±CT vs. CT	OS	A: OS, 39.5 vs. OS, 24.8 months (P<0.001) B: OS, 39.5 vs. OS, 27.8 months (P<0.001)	(25)
Liao *et al* 2013	9 RCTs	A: CT (F) vs. OBS B: CT (G) vs. OBS C: CRT vs. OBS D: CRT+F vs. OBS E: CRT+G vs. OBS	OS	A: HR, 0.62 (95% CI, 0.42-0.88) B: HR, 0.59 (95% CI, 0.41-0.83)[a] C: HR, 0.91 (95% CI, 0.55-1.46) D: HR, 0.54 (95% CI, 0.15-1.80) E: HR, 0.44 (95% CI, 0.10-1.81)	(22)
Yu *et al* 2013	4 RCTs	CT (G) vs. OBS or CT (F/FA)	OS	Overall HR, 0.88 (95% CI, 0.72-0.94, P=0.014)	(23)
Ren *et al* 2012	15 RCTs	A: CT vs. OBS B: CRT vs. OBS	OS, DFS	A: OS OR, 1.98; P<0.001; DFS OR, 2.12; P<0.001 B: OS OR, 0.99; P=0.93; DFS OR, 0.99; P=0.95	(24)
Butturini *et al* 2008	4 RCTs	A: CT vs. OBS B: CRT vs. OBS	OS	A: R0 HR, 0.65 (95% CI, 0.53-0.80); R1 HR, 1.04 (95% CI, 0.78-1.40) B: R0 HR, 1.19 (95% CI, 0.95-1.49); R1 HR, 0.72 (95% CI, 0.47-1.10)	(21)
Boeck *et al* 2007	5 RCTs	CT vs. OBS	Improvement in median survival	3-month improvement (95% CI, 0.3-5.7; P=0.03)	(20)
Khanna *et al* 2006	4 RCTs, 1 PS	A: CT±RT vs. OBS B: CRT vs. OBS	Improvement in 2-year survival	A: 12% improvement (95% CI, 3-21; P=0.011) B: 12% improvement (95% CI, 2-22; P=0.022)	(26)
Stocken *et al* 2005	5 RCTs	A: CT vs. OBS B: CRT vs. OBS	OS	A: HR, 0.75 (95% CI, 0.64-0.90, P=0.001) B: HR, 1.09 (95% CI, 0.89-1.32, P=0.43)	(19)

[a]Following adjustment for confounding factors. CRT, chemoradiotherapy; OBS, observation; CT, chemotherapy; OS, overall survival; RCTs, randomized controlled trials; F, 5-fluorouracil; G, gemcitabine; HR, hazard ratio; CI, confidence interval; FA, folinic acid; DFS, disease-free survival; OR, odds ratio; R0, negative-margin resection patients; R1, microscopically positive-margin resection patients; PS, prospective study (non-randomized); RT, radiotherapy.

Table II. Meta-analyses of neoadjuvant therapy in localized, borderline resectable or locally advanced pancreatic cancer.

Study	Included trials	Analytic arm(s)[a]	Main end point(s)	Findings	(Refs.)
Petrelli *et al* 2014	2 phase II, 11 retrospective	FOLFIRINOX + CRT (BR/LAPC)	Resectability rate, R0 resection rate	43% resectable (95% CI, 32.8-53.3); 39.4% R0 resection rate (95% CI, 32.4-46.9)	(49)
Xu *et al* 2014	1 PS, 2 retrospective	CRT vs. adjuvant CRT (LPC)	OS	Pooled HR 0.93 (95% CI, 0.69-1.25; P=0.62)	(41)
Festa *et al* 2013	5 phase II, 5 PS	CT ± RT (BR)	Resectability rate, 1- and 2-year survival rate after resection	69% explored (95% CI, 56-80); 80% of explored resected (95% CI, 66-90); 1-year, 61% (95% CI, 48-100); 2-year, 44% (95% CI, 32-59)	(53)
Andriulli *et al* 2012	7 phase I/II, 10 phase II, 3 PS	A: CT (G) ± RT (LPC) B: CT (G) ± RT (BR/LAPC)	1- and 2-year survival rate after resection, resectability rate	A: 1-year, 91.7% (95% CI, 75-100); 2-year 67.2% (95% CI, 38-87); 91% explored (95% CI, 83-97); 82% of explored resected (95% CI, 65-95) B: 1-year 86.3% (95% CI, 78-100); 2-year 54.2% (95% CI, 25-100); 39% explored (95% CI, 28-50); 68% of explored resected (95% CI, 53-82)	(38)
Assifi *et al* 2011	14 phase II	A: CT ± RT (LPC) B: CT ± RT (BR/LAPC)	Resectability rate, OS after resection	A: 65.8% resectable (95% CI, 55.4-75.6); median OS 23.0 months (11.7-34 months) B: 31.6% resectable (95% CI ,14.0-52.5); median OS 22.3 months (18-26.3 months)	(40)
Laurence *et al* 2011	9 PS or retrospective	A: CRT vs. without CRT (LPC) B: CRT vs. without CRT (BR/LAPC)	1- and 2-year survival after resection	A: 1-year OR 0.49 (95% CI, 0.22-1.13; P=0.09) B: 1-year OR 0.56 (95% CI, 0.39-0.80; P=0.001); 2-year OR 1.03 (95% CI, 0.70-1.51; P=0.89)	(48)
Gillen *et al* 2010	15 phase I, 13 phase I/II, 28 phase II, 14 cohort, 41 CS	A: CT ± RT (LPC) B: CT ± RT (BR/LAPC)	Resectability rate, OS after resection	A: 73.6% resectable (95% CI, 65.9-80.6); median OS 23.3 months (12-54 months) B: 33.2% resectable (95% CI, 25.8-41.1); median OS 20.5 months (9-62 months)	(39)
Morganti *et al* 2010	10 PS, 3 retrospective	CRT (BR/LAPC)	Resectability rate, OS after resection	8.3-64.2% resectable (median 26.5%); median OS 23.6 months (16.4-32.3 months)	(47)

[a]Therapeutic arms are in the neoadjuvant setting, unless otherwise stated. FOLFIRINOX, 5-FU, leucovorin, irinotecan, and oxaliplatin; CRT, chemoradiotherapy; BR, borderline resectable pancreatic cancer; LAPC, locally advanced pancreatic cancer; R0, negative-margin; CI, confidence interval; PS, prospective study; LPC, localized pancreatic cancer; OS, overall survival; HR, hazard ratio; CT, chemotherapy; RT, radiotherapy; G, gemcitabine; OR, odds ratio; CS, case series.

been proposed that resection should proceed following neoadjuvant therapy in the absence of disease progression or a decline in performance status (PS) (52,53). Regardless, neoadjuvant therapy, ideally in the context of a clinical trial, is now recommended for borderline resectable disease in the absence of treatment criteria that has yet to be clearly defined (8). Recently, more intensive neoadjuvant regimens involving induction gemcitabine/nab-paclitaxel or 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have been used (5,37,54). In particular, induction FOLFIRINOX ± chemoradiation followed by surgery has shown a significantly increased survival rate compared to those with locally advanced/borderline resectable disease who received no neoadjuvant therapy (55). The ongoing Alliance A021101 multi-institutional trial (NCT01821612) using induction modified FOLFIRINOX (mFOLFIRNOX) and chemoradiotherapy followed by resection and adjuvant therapy will attempt to standardize a uniform definition of borderline resectable PDAC and criteria for assessing treatment efficacy.

Systemic and locoregional therapy. Low quality evidence from meta-analyses suggests that surgical resection appears to improve survival, decrease the length of hospital stay, and decrease costs compared to palliative treatment in select patients with locally advanced pancreatic cancer (LAPC) with venous involvement (56). Despite more aggressive approaches, such as pancreatectomy with arterial reconstruction (AR), having demonstrated improved survival over those without resection, higher perioperative morbidity/mortality rates and poorer long-term survival were observed with pancreatectomy + AR compared to pancreatectomy with venous reconstruction in those with LAPC (57). However, chemotherapy remains a critical component of the treatment approach for attempting to downstage locally advanced disease or palliative treatment of tumors that cannot be downstaged and resected, or those for which surgery is not an option. Early evidence demonstrated that chemotherapy (5-FU-based) improves survival compared to best supportive care alone, although 5-FU-based combination chemotherapy did not result in an increased survival compared to 5-FU alone in advanced pancreatic cancer (APC) (58). Gemcitabine widely became regarded as the preferred first-line therapy in APC due to its superiority over 5-FU (as discussed in the following) (59). A majority of meta-analyses on gemcitabine in combination with various agents, such as platinums, anthracyclines, camptothecin analogs, fluoropyrimidines, taxanes and molecular-targeted agents (MTAs), have since shown that gemcitabine-based combination therapy, in general, often results in greater toxicity yet appears to significantly improve OS, progression-free survival (PFS), and/or overall response rates (ORRs) compared to gemcitabine monotherapy in locally advanced/metastatic pancreatic cancer (Table III) (58,60-73).

Subgroup and pooled analyses further reveal that gemcitabine + fluoropyrimidine (particularly capecitabine) and gemcitabine + platinum combinations represent the gemcitabine-based doublets providing the most consistent survival benefits over gemcitabine alone (58,63-73). Of note, gemcitabine + cisplatin appears to offer little to no significant survival benefits versus gemcitabine monotherapy, although others have contended this claim (61,65,68,70,72,73). In addition, gemcitabine + camptothecin analog appears to only improve the ORR over single-agent gemcitabine (65). Although one subgroup analysis showed that gemcitabine + MTAs was the only combination resulting in a significant improvement in 6-month survival over gemcitabine alone, a number of meta-analyses have produced inadequate results with the exception of epidermal growth factor receptor (EGFR) inhibitors, such as erlotinib (discussed in the following) in locally advanced/metastatic disease (63,65,73-78). S-1 has been studied extensively in Japanese patients with pancreatic cancer (79-81). In the locally advanced setting, there is conflicting data to support the use of S-1 in combination with gemcitabine. Consensus remains that this is an active agent for Asian patients; however, it requires further validation prior to adoption in the US as pharmacogenomic differences between ethnicities have been noted and may explain the varying reports of efficacy and toxicity of S-1 and other 5-FU based drugs (73).

In LAPC, survival trends favor gemcitabine-based combination regimens over gemcitabine alone (82). Combination therapy appears to have its greatest effects on survival in those with good PS [Eastern Cooperative Oncology Group (ECOG) scores of 0-1]; however, is relatively ineffective or even harmful in those with poor PS (ECOG ≥2) (68,70,72).

Due to the survival benefits demonstrated in borderline resectable/LAPC and metastatic pancreatic cancer (MPC), intensive regimens, such as FOLFIRINOX or gemcitabine/nab-paclitaxel, are now being recommended in those with good PS (ECOG 0-1), while gemcitabine monotherapy remains the mainstay of therapy in those with poor PS (ECOG ≥2); the National Comprehensive Cancer Network, however, states gemcitabine monotherapy as an acceptable option in those with good PS and LAPC (55,83-85). There are still no phase III trials comparing FOLFIRINOX to gemcitabine/nab-paclitaxel in LAPC. Other meta-analyses have addressed gemcitabine dosing, delivery of chemotherapy (intra-arterial versus venous), and innovative ablative therapies as additional avenues of clinical benefit in LAPC/APC (86-89).

The role of chemoradiation in the management of LAPC remains controversial. Key trials involving chemoradiotherapy have produced mixed results with regards to survival advantage versus standard therapies in LAPC/APC (90-96). Chemoradiation confers a survival advantage over best supportive care alone or radiotherapy alone; however, it is more toxic (97-99). Furthermore, meta-analyses demonstrate that primarily 5-FU or gemcitabine-based chemoradiotherapy ± prior induction chemotherapy ± maintenance chemotherapy offers comparable or even superior survival times compared to chemotherapy alone, although often with greater toxicities in LAPC (Table III) (97-101). Notably, one analysis showed better survival with gemcitabine-based chemoradiation compared to 5-FU-based chemoradiation, although other studies have argued that capecitabine or 5-FU are the preferred radiosensitizers in LAPC (84,98,102). Upfront chemoradiotherapy initially lost acceptability with the FFCD/SFRO trial when induction 5-FU + cisplatin chemoradiation followed by maintenance gemcitabine showed inferior survival and greater toxicity compared to gemcitabine alone (96). However, several

Table III. Meta-analyses of conventional systemic and locoregional therapy in locally advanced, advanced, or metastatic pancreatic cancer.

Study	Trials	Analytic arm(s)	Main end point(s)	Findings	(Refs.)
Bernstein *et al* 2014	6 RCTs	CRT vs. CT	OS	HR 0.88 (95% CI, 0.67-1.15; P=0.351)	(100)
Chan *et al* 2014	16 RCTs	Bayesian analysis	OS	Best regimen probability 83% FOLFIRINOX, 11% G-nab, 3% G + erlotinib	(114)
Gresham *et al* 2014	23 RCTs	Combo-CT vs. G alone	OS	Combo-CT superior to G alone (including FOLFIRINOX and G-nab)	(115)
Li *et al* 2014	8 RCTs	G+fluorouracil drugs vs. G alone	OS, ORR	G + fluorouracil drugs significantly improved OS, ORR compared to G alone	(67)
Petrelli *et al* 2014	29 RCTs	Combo-CT vs. G alone	OS	HR 0.87 (95% CI, 0.81-0.93; P<0.0001)	(116)
Zhang *et al* 2014	3 RCTs, 1 RS	G-based CRT vs. G alone	OS	HR 0.84 (95% CI, 0.53-1.34; P=0.48)	(101)
Chen *et al* 2013	15 RCTs	A: CRT vs. RT B: CRT vs. CT	6-, 12- and 18-months OS	A: 6-, 12- and 18-months (all P<0.01) B: 6-, 12- and 18-months (all P>0.05)	(99)
Ciliberto *et al* 2013	34 RCTs	G-combo vs. G alone	OS	HR 0.93 (95% CI, 0.89-0.97; P=0.001)	(73)
Yang *et al* 2013	5 RCTs, 9 PS, 2 RS	G + erlotinib	PFS, OS	PFS 2-9.6 months; OS 5-12.5 months	(110)
Sun *et al* 2012	26 RCTs	G-combo vs. G alone	1-year OS	RR 0.90 (95% CI, 0.82-0.99; P=0.04)	(66)
Hu *et al* 2011	35 RCTs	G-combo vs. G alone	OS, PFS	OS OR 1.15 (P=0.011); PFS OR 1.27 (P<0.001)	(65)
Zhu *et al* 2011	3 RCTs, 1 RS	G-based CRT vs. F-based CRT	12-months OS	G-based CRT superior to F-based CRT, 12-months OS RR 1.54 (95% CI, 1.05-2.26; P=0.03)	(102)
Xie *et al* 2010	18 RCTs	Subgroup analysis of 5 G-combo regimens	6-months OS	G-C 6-months OS RR 0.85 (P=0.04); G-Ox 6-months OS RR 0.80 (P=0.001)	(72)
Cunningham *et al* 2009	3 RCTs	G-C vs. G alone	OS	HR 0.86 (95% CI, 0.75-0.98; P=0.02)	(71)
Huguet *et al* 2009	2 MAs, 13 RCTs, 2 NRTs	A: CRT vs. BSC or RT B: CRT vs. CT	OS	A: CRT superior to BSC or RT alone B: CRT not superior to CT	(98)
Heinemann *et al* 2008	15 RCTs	G-combo vs. G alone	OS	HR 0.91 (95% CI, 0.85-0.97; P=0.004)	(70)
Sultana *et al* 2008	11 RCTs	Indirect analysis of 4 G-combo regimens	OS	No significant difference in survival	(82)
Sultana *et al* 2008	51 RCTs	A: F-combo vs. F alone B: G-combo vs. G alone	PFS/TTP	A: TTP HR 1.02 (95% CI, 0.85-1.23) B: PFS HR 0.78 (95% CI, 0.70-0.88)	(62)
Banu *et al* 2007	23 RCTs	G-D vs. G alone	OS	12-months RRR 4% (95% CI, 1-7); 18-months RRR 2% (95% CI, 1-4), P<0.05 in both	(69)
Bria *et al* 2007	20 RCTs	G-combo vs. G alone	OS	No significant difference in survival	(64)
Heinemann *et al* 2007	2 RCTs	G-P vs. G alone	OS, PFS	OS HR 0.81 (P=0.031); PFS HR 0.75 (P=0.0030)	(68)
Sultana *et al* 2007	51 RCTs	A: CT vs. BSC B: F-combo vs. F alone	OS	A: HR 0.64 (95% CI, 0.42-0.98) B: HR 0.94 (95% CI, 0.82-1.08)	(58)
Sultana *et al* 2007	11 RCTs	A: CRT vs. RT B: CRT followed by CT vs. CT	OS	A: HR 0.69 (95% CI, 0.51-0.94) B: HR 0.79 (95% CI, 0.32-1.95)	(97)
Xie *et al* 2006	6 RCTs	G-DDP vs. G alone	OS, CBR	No significant difference in survival or CBR	(61)

Table III. Continued.

Study	Trials	Analytic arm(s)	Main end point(s)	Findings	(Refs.)
Xie *et al* 2006	22 RCTs	G-combo vs. G alone	1-year survival and 6-months PFS rate	1-year RD 3% (95% CI, 0.01-0.05; P=0.01); 6-months PFS rate RD 7% (95% CI, 0.04-0.10; P<0.00001)	(63)
Liang *et al* 2005	19 RCTs	G-combo vs. G alone	6-months survival and PFS rate	6-months survival rate RD 4% (P=0.02); 6-months PFS rate RD 10% (P=0.00001)	(60)
Fung *et al* 2003	43 RCTs	CT (F-based) vs. BSC	OS	CT (F-based) superior to BSC alone	(108)

RCTs, randomized controlled trials; CRT, chemoradiotherapy; CT, chemotherapy; OS, overall survival; HR, hazard ratio; CI, confidence interval; FOLFIRINOX, 5-FU, leucovorin, irinotecan, and oxaliplatin; G-nab, gemcitabine + nab-paclitaxel; Combo-CT, combination chemotherapy; G, gemcitabine; ORR, overall response rate; RS, retrospective study; RT, radiotherapy; G-combo, gemcitabine-based combination chemotherapy; PS, prospective study; PFS, progression-free survival; RR, risk ratio; OR, odds ratio; F, 5-fluorouracil (5-FU); G-C, gemcitabine + capecitabine; G-Ox, gemcitabine + oxaliplatin; MAs, meta-analyses; NRTs, non-randomized trials; BSC, best supportive care; F-combo, 5-FU-based combination chemotherapy; TTP, Time to progression; G-D, gemcitabine-based doublets; RRR, relative risk reduction; G-P, gemcitabine + platinum; G-DDP, gemcitabine + cisplatin; CBR, clinical benefit rate; RD, risk difference (risk in gemcitabine-based combination group - risk in gemcitabine alone).

studies revealed that induction gemcitabine-based chemotherapy followed by consolidation 5-FU, capecitabine or gemcitabine-based chemoradiation, when there was no evidence of disease progression after 2 months of initial chemotherapy, provided favorable survival outcomes (even greater than in those who received chemoradiation or chemotherapy alone) in LAPC (103-105).

The rationale for this approach is associated with the fact that ~30% of those with LAPC have occult metastatic disease at diagnosis, and induction chemotherapy can identify the subset of patients without metastatic disease who can benefit from locoregional control or those with aggressive disease who can be spared from resection and the toxicities of chemoradiotherapy (84,85). Ultimately, radiotherapy alone or upfront chemoradiotherapy is not recommended as standard treatment for LAPC, although upfront chemoradiotherapy is an option in those with poorly controlled pain, bleeding or local obstruction (84,85). Consolidation chemoradiation remains a recommended option for those with LAPC and good PS without evidence of disease progression following 2-6 cycles or 3-4 months of induction chemotherapy, despite preliminary results from the phase III LAP 07 study indicating no survival benefit with additional chemoradiation after induction gemcitabine compared to chemotherapy alone (84-85,106). Modern radiotherapy techniques with concurrent chemotherapy also represent a relatively cost-effective strategy in improving clinical outcomes in LAPC (107).

4. Advanced and metastatic pancreatic cancer (stage IV)

Systemic therapy. The remaining ~50% of patients with pancreatic cancer present with advanced or metastatic disease (stage IV) with a median survival of 4-6 months and approximate 5-year survival rates of 1-2% (1,4,45). Treatment remains palliative for this group with gemcitabine having been the mainstay of therapy for the majority of the late 1990s and early 2000s; gemcitabine remains the first-line therapy in those with poor PS and MPC. For the last 3 decades of the 20th century, 5-FU was superior to best supportive care (108). A seminal trial in 1997 indicated a superior clinical benefit and a survival advantage with gemcitabine (median OS, 5.65 months) compared to 5-FU (median OS, 4.41 months, P=0.0025) in APC (59). In 2007, gemcitabine/erlotinib showed a small survival benefit leading to Food and Drug Administration approval of its use in APC (109,110). Again, S-1 alone proved to be noninferior to gemcitabine alone in an Asian-based phase III trial (111). More recently, FOLFIRINOX and gemcitabine/nab-paclitaxel both independently conferred significant survival advantages over gemcitabine alone (112,113). Meta-analyses suggest that FOLFIRINOX and gemcitabine/nab-paclitaxel have the highest probabilities for being the two best regimens in terms of OS and PFS for APC, despite their increased risk for greater toxicities (Table III) (114-116). FOLFIRINOX demonstrates favorable cost-effectiveness and greater quality adjusted life-years compared to gemcitabine as first-line therapy (117). FOLFIRINOX and gemcitabine/nab-paclitaxel appear to have changed the standard of care, at least in those with good PS, as 2-year survival rates are now approaching 10% for either agent in advanced/metastatic disease-survival rates that were rarely observed previously (5).

5. Conclusion

Pancreatic cancer remains the most lethal of the common cancers with a 5-year survival rate across all stages of ~6.7% (1). Meta-analyses confirm that adjuvant gemcitabine or 5-FU improves survival compared to surgery alone and remains the standard for adjuvant therapy in resected pancreatic cancer. Although the benefits from the addition of radiation therapy in the adjuvant setting are under debate, 5-FU-based or gemcitabine-based chemoradiation preceded or followed by 5-FU/leucovorin or gemcitabine remains an acceptable alternative form of adjuvant therapy in resected pancreatic cancer. Meta-analyses demonstrate high rates of resectability with neoadjuvant therapy (FOLFIRINOX ± chemoradiation) in those with borderline resectable disease, although treatment criteria has yet to be clearly defined in this group. When applicable, neoadjuvant therapy in the context of a clinical trial is recommended for borderline resectable pancreatic cancer. For locally advanced and unresectable disease, meta-analyses confirm the benefits of combination chemotherapy over single-agent chemotherapy. FOLFIRINOX or gemcitabine with nab-paclitaxel are now being recommended in those with good PS while gemcitabine alone is recommended in those with poor PS in LAPC. Induction chemotherapy followed by chemoradiotherapy remains an option in certain patients with LAPC. In stage IV disease, meta-analyses confirm the survival benefits offered by FOLFIRINOX or gemcitabine with nab-paclitaxel compared to gemcitabine alone and are now treatment standards in those with good PS. Gemcitabine remains an option in patients with metastatic pancreatic cancer and poor PS. Despite the poor prognosis, development of novel therapeutic agents, advancements in diagnosis and prevention, and improvements in multidisciplinary care are underway in order to enhance outcomes in this area (4,5,7). Improved survival is currently being observed postoperatively and in advanced/metastatic disease with greater implementation of adjuvant and intensive multi-agent therapies, respectively. However, the results from ongoing clinical trials covering all stages of management in pancreatic cancer, including neoadjuvant, adjuvant and palliative therapy, are anticipated.

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