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REVIEW

Multidisciplinary neoadjuvant management for potentially curable pancreatic cancer

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Abstract

Pancreatic adenocarcinoma remains the fourth leading cause of cancer mortality in the U.S. Despite advances in surgical technique, radiotherapy technologies, and chemotherapeutics, the 5-year survival rate remains approximately 20% for the 15% of patients who are eligible for surgical resection. The majority of this group suffers metastatic recurrence. However, despite advances in therapies for patients with advanced pancreatic cancer, only surgery has consistently proven to improve long-term survival. Various combinations of chemotherapy, biologic-targeted therapy, and radiotherapy have been evaluated in different settings to improve outcomes. In this context, a neoadjuvant (preoperative) treatment strategy offers numerous potential benefits: (1) ensuring delivery of early, systemic therapy, (2) improving selection of patients for surgical therapy with truly localized disease, (3) potential downstaging of the neoplasm facilitating a negative margin resection in patients with locally advanced disease, and (4) providing a superior clinical trial mechanism capable of rapid assessment of the efficacy of novel therapeutics. This article reviews the recent trends in the management of pancreatic adenocarcinoma, with a particular emphasis on a multidisciplinary neoadjuvant approach to treatment.

Background

Pancreatic adenocarcinoma is the fourth leading cause of cancer deaths in the United States [1]. The annual incidence of pancreatic cancer is rising with approximately 46,420 new cases and nearly 39,590 patient deaths in 2014 [2]. Without any substantive improvement in curative therapies, it is anticipated to be the second leading cause of cancer deaths by 2030 [3]. Surgical resection is currently the only treatment option that offers the potential of long-term survival. However, only 20% of patients with pancreatic cancer are candidates for resection. Another 30–40% of patients have locally advanced or unresectable pancreatic cancer without measurable metastatic disease. For this group, chemotherapy with radiotherapy (chemoRT) was established as the standard of care over radiation or chemotherapy alone a few decades ago by the Gastrointestinal Tumor Study Group (GITSG) [4, 5]. For these patients, chemotherapy with radiation is palliative in nature with a median survival of 8–12 months and virtually no long-term survivors [6, 7]. Of the patients that present with resectable disease, surgical resection provides a 5-year survival of approximately 20%. This article focuses on the recent advances made in combined modality treatment of early stage resectable and borderline-resectable pancreatic adenocarcinoma with the goal of making a compelling case for a multidisciplinary, collaborative, and neoadjuvant approach for optimal outcomes. This strategy also facilitates an ideal clinical research platform capable of rapidly assessing the efficacy of novel therapeutic agents.

Role of Adjuvant Therapy in Pancreatic Cancer

Despite improvements in surgical techniques that allow more patients to undergo successful R0 resection, the prognosis even for small tumors without nodal involvement remains poor due to progressive systemic disease. In an effort to improve long-term survival after surgical resection, adjuvant therapy has been studied in various combinations. In 1985, the GITSG conducted a trial that was one of the first to show the benefit of adjuvant therapy by demonstrating that 5-Fluorouracil (5-FU) combined with radiotherapy (RT) after surgical resection led to improved survival compared to observation (2-year survival 42% vs. 15%; $P = 0.03$) [8]. The EORTC 40891 trial similarly compared 5-FU-based chemoRT to observation after surgical resection of pancreatic and periampullary adenocarcinoma with median overall survival (OS) of 24.5 versus 19 months ($P = 0.21$) [9]. One of the major criticisms of the latter study was that it included periampullary adenocarcinomas, which have a better prognosis compared to pancreatic ductal adenocarcinomas. The rationale for adjuvant chemoRT was established with these early studies.

The role of adjuvant chemoRT was subsequently called into question in the European ESPAC-1 trial [10]. Following surgical resection, patients were randomized to either receive 5-FU-based chemotherapy, 5-FU-based chemoRT, both or no treatment following surgical resection. Results were analyzed (in a two-by-two factorial design) based on groups having received chemotherapy or not and those having received chemoRT or not. Median OS in the chemotherapy group was 20.1 versus 15.5 months in the no chemotherapy group ($P = 0.009$). However, in the chemoRT analysis, the median OS was worse at 15.9 months compared to 17.9 months in patients who did not receive chemoRT ($P = 0.05$). This controversial trial is criticized for the lack of radiation quality control, use of outdated radiotherapy delivery techniques, no central review of radiographic response and poor compliance to subscribed treatment. Such limitations confound the ability to accurately and conclusively interpret the results. Nevertheless, the utilization of adjuvant chemoRT remains common in the United States with the benefit of this approach continuing to be actively investigated.

Subsequent European adjuvant clinical trials focused on the relative value of adjuvant chemotherapy rather than chemoRT. In the CONKO-1 trial, patients with resected pancreatic cancer were randomly assigned to either receive six cycles of gemcitabine or observation [11]. The use of adjuvant gemcitabine resulted in significant gains in disease-free survival (DFS) from 6.7 to 13.4 months ($P < 0.001$) and a significant, albeit small, improvement in OS from 20.2 to 22.8 months ($P = 0.01$). Following this trial, the ESPAC-3 study compared adjuvant gemcitabine to 5-FU-based chemotherapy for 6 months [12]. Median OS was not statistically different between the two treatment groups (23.6 vs. 23 months; P = NS). The overall rates of serious adverse events were significant reduced in the gemcitabine group (7.5%) compared to 5-FU-based treatment (7.5% vs. 14%; $P < 0.001$), with the toxicity profile also favoring gemcitabine with less stomatitis and diarrhea but more myelosuppression.

In the United States, the incorporation of adjuvant chemoRT continues to be investigated with trials designed to determine the optimal chemotherapy agents and sequencing for use in combination with radiotherapy. The RTOG 97-04 trial compared gemcitabine to 5-FU in a sequential combination of systemic chemotherapy (gemcitabine vs. 5-FU) for 3 weeks followed by 5-FU-based chemoRT and then 3 months of chemotherapy with the same previously used agent. Median OS was 20.5 months for gemcitabine versus 16.9 months for 5-FU ($P = 0.09$) [13]. The above trials suggest that whether combined with radiation or not, gemcitabine may be a preferred agent in the adjuvant setting given a better side-effect profile; whereas 5-FU remains the next best option.

Adjuvant Versus Neoadjuvant Debate

Despite the noted improvements in survival with the addition of adjuvant therapy, the 5-year OS still averages 20% in patients who undergo curative treatment, leaving significant opportunities for improvement. This has led to an increasing interest to incorporate chemotherapy and/or radiation therapy into the neoadjuvant setting. Neoadjuvant treatment may have several advantages over adjuvant therapy (Table 1). First, as the vast majority of

Table 1. Potential advantages and disadvantages of neoadjuvant treatment in pancreatic adenocarcinoma.

Neoadjuvant treatment	
Advantages	Disadvantages
Intact tumor vasculature not disrupted by surgery	Progression of disease during neoadjuvant treatment leading to missed window of opportunity for resection
Early treatment of micrometastatic disease	Toxicity from neoadjuvant treatment precluding definitive surgical resection
Ensures delivery of systemic treatment	Need tissue confirmation of neoplastic process
Improved RO resection rate; especially in borderline-resectable cases	
Ideal in vivo platform for research	

patients who undergo complete surgical resection still succumb to distant relapse, delivery of systemic treatment earlier in the disease course; particularly, when the anatomy and vasculature have not yet been disrupted by surgery, might lead to improved treatment effect. Second, almost 30–40% of postoperative patients do not receive any adjuvant therapy either secondary to surgical complications and delayed recovery or patient refusal [14]. Third, tumor downstaging resulting from effective neoadjuvant treatment could lead to more effective R0 (complete) resections, which has been shown to be a predictor of survival [15]. However, tumor downstaging requires accurate confirmation of the clinical stage prior to initiation of therapy, which is limited by the accuracy of current imaging modalities. Finally, the neoadjuvant platform is perhaps the most efficient *in vivo* model to test novel therapies as the treatment period is finite and pre/posttreatment tissue collection allows for a variety of molecular analyses to gain further insight into tumor biology and mechanisms of resistance. Opponents of neoadjuvant treatment voice concerns that the use of preoperative therapy can lead to a missed window of opportunity for surgical resection, which is the only potentially curative treatment. Such missed opportunities can result from progression of disease (typically distant metastases) or a decline in performance status from treatment toxicities or cancer cachexia. However, the issue of disease progression can also be seen as a paradoxical benefit given the morbidity of a major operative procedure such as pancreaticoduodenectomy in a patient with a biologically aggressive disease that might have likely relapsed soon after surgery. However, delaying surgical resection due to performance status decline from treatment side effects remains a legitimate concern. While no phase III trials exist, several retrospective series, prospective phase II, and systematic reviews have been published which provide some data with regards to neoadjuvant therapy outcomes.

Neoadjuvant Treatment of Pancreatic Cancer

The concept of incorporating neoadjuvant therapy into pancreatic cancer management started soon after early studies demonstrated a benefit of adjuvant treatment as compared to surgery alone. As early as 1980, Pipelich et al. showed that preoperative radiotherapy was not only feasible but allowed for downstaging of primary tumors and thus successful surgical resection [16]. Since then, various combinations of chemotherapy, chemoRT or induction chemotherapy followed by chemoRT have been studied in relatively small phase I–II trials.

Early studies focused on 5-FU-based treatment combinations. The combination of 5-FU and mitomycin C (MMC) with external beam radiotherapy (EBRT) was particularly popular at that time. This was in part related to the widespread availability of the agents and their well-established role as potent radiosensitizers. Most of these trials consistently showed superior survival with the use of neoadjuvant treatment in resected patients as compared to historical controls who only received surgical resection. However, the direct impact of this treatment modality on resection rates is difficult to quantify for several reasons. First, the preoperative imaging quality during that time was limited in determining resectability. Second, even in cases where resectability status was based on laparotomy, there was institutional and surgeon variability with regards to expertise and definitions of resectability. While most of these studies demonstrated safety and feasibility, some showed survival comparable to that of studies involving adjuvant therapy. One such study by Hoffman et al. in 1995 included patients with both unresectable and resectable pancreatic cancers of adenocarcinoma and adenosquamous histology [17]. Patients received preoperative 5-FU plus MMC with concurrent radiotherapy. The resection rate for all patients was 32% with resected patients having a reported median survival of 45 months; which is almost twice as long as reported in other studies. Promising as these results appear, it is hard to apply data from such small, single arm, single institution studies due to inherent selection bias and the heterogeneity of the study population.

In the decade following, gemcitabine-based neoadjuvant combinations gained popularity due to the positive findings reported by Burris and colleagues in the metastatic setting with regards to clinical benefit as well as a modest survival advantage [18]. As a result of that latter study, gemcitabine received FDA approval and has become an established standard of care in advanced disease and in the adjuvant setting. The most frequently used neoadjuvant combinations were gemcitabine with or without an additional agent (including radiotherapy in some studies). The resection rate was noted to be variable depending on the initial resectability status of the patients enrolled. In the earlier trials, the overall resection rate after neoadjuvant therapy for patients who were deemed to have resectable disease upfront ranged from 50% to 70%. For those patients judged to be unresectable at the time of enrollment, the overall resection rate after neoadjuvant treatment ranged from 5% to 30%. More recent trials have shown an improved trend in both resection rates and survival for patients resected after preoperative treatment. In the modern era of studies, patients initially deemed resectable have resection rates in the 60–80% range with OS improving from 20 to 30 months for those patients receiving preoperative therapy. However, most of these studies were single institution or retrospective in design.

In an initial phase II trial from MD Anderson Cancer Center, 86 patients with resectable, histologically proven adenocarcinomas of pancreatic head or uncinate process were treated with neoadjuvant therapy [19]. These patients underwent preoperative treatment with gemcitabine weekly for 7 weeks along with 30 Gy of EBRT over 2 weeks. The overall resection rate was 74%, (57/64 patients had R0 resections) with median survival of those patients undergoing resection noted to be 34 months. However, the majority of cases that relapsed did so with distant metastases. Therefore, in an attempt to improve the OS, Varadhachary and colleagues incorporated more systemic therapy by adding induction chemotherapy with gemcitabine plus cisplatin for four doses followed by chemoRT using gemcitabine weekly with 30 Gy EBRT [20]. Of the 90 patients enrolled, 79 were able to complete neoadjuvant treatment. The overall resection rate for these 79 patients was 66% (51/52 patients had R0 resections) with median OS for those resected being 31 months. Memorial Sloan-Kettering Cancer Center treated 38 patients with gemcitabine with oxaliplatin for four cycles neoadjuvantly [21]. Thirty-five patients (92%) completed neoadjuvant chemotherapy; 27 were ultimately resected (72%) and 23 (60.5%) were able to complete all planned treatments including additional adjuvant chemotherapy. Median OS was 27.2 months suggesting improvement in ability to complete the delivery of multimodality therapy. Additional prospective and retrospective neoadjuvant trials are summarized in Table 2.

Given the risk of incomplete resection, neoadjuvant chemotherapy may similarly improve outcomes in borderline-resectable pancreatic cancer. In a retrospective report from Massachusetts General Hospital, 46 patients with unresectable and 24 patients with borderline-resectable disease were treated with neoadjuvant fluoropyrimidine-based chemoRT. Approximately 30 of these patients additionally received gemcitabine-based chemotherapy sequenced before the chemoRT. Compared with chemoRT alone, the use of neoadjuvant chemotherapy before chemoRT achieved improved median overall (18.7 vs. 12.4 months; $P = 0.02$) and progression-free survival (11.4 vs. 6.7 months; $P = 0.02$) [22].

The development of novel targeted or more contemporary cytotoxic therapeutics in metastatic pancreatic cancer was also investigated in the neoadjuvant setting. In a retrospective large single center study by Strobel and colleagues, 257 patients received neoadjuvant chemotherapy or chemoradiation [23]. Only 120 (46.7%) underwent successful resection. Median postoperative survival was highest at R0 resected patients (24.6 months) compared to R1 (11.9 months) and R2 (8.9 months) demonstrating that margin status at surgery is still a major determinant of outcome, even with contemporary neoadjuvant therapy. The incorporation of FOLFIRINOX chemotherapy in the neoadjuvant setting has been explored in relatively small pilot studies. Boone and colleagues at the University of Pittsburgh treated 21 unresectable and borderline-resectable patients with this regimen. Two patients (9%) could not tolerate treatment and another three (14%) had disease progression. Overall, seven patients ultimately underwent resection of which 2 (10%) were initially unresectable and were felt to have been converted. Five (24%) of the treated and resected patients had significant histopathological response [24]. Massachusetts General investigators treated 22 locally advanced pancreatic cancer patients in this manner with five of 22 patients achieving R0 resections after completing FOLFIRINOX, 5FU-based chemoradiation and surgical resection. However, three had distant recurrence and toxicity was significant with this approach [25].

While it is clear from the published studies that neoadjuvant therapy for pancreatic cancer appears feasible, the demonstrated benefits have been inconsistent. One of the primary limitations of these studies has been the use of historical controls as a comparison group. Over the intervening years, imaging technology has become increasingly accurate in delineating vessel involvement by pancreatic cancer, which is a major barrier to successful surgical resection. Indeed, such stage migration will, by definition, improve the apparent survival of patients newly diagnosed with both resectable as well as locally advanced pancreatic cancer. Similarly, advances in surgical techniques with more sophisticated vascular reconstruction capabilities, have also impacted the ability to obtain complete resections. However, it is not clear if complete resection in these borderline or previously unresectable patients with the use of modern vascular reconstruction techniques affords a similar long-term benefit as a complete resection in an initially clearly resectable patient. Another limitation includes an evolving definition of resectable disease. Surgical perspective by the treating physician adds a nongeneralizable bias to patient selection in regards to generating a homogenous treatment group as well as appropriate control matching. Only recently has a consistent definition been applied to studies, thus allowing cross-study comparisons. The summary data of neoadjuvant treatments (Table 2) inventories the outcomes of patients organized by resectable, borderline resectable, and unresectable disease.

Further confounding the response of neoadjuvant treatment was a publication by the MD Anderson group. These authors reported that routine imaging does not reflect anatomic-pathologic changes associated with the effectiveness of neoadjuvant therapy [26]. This retrospective study reviewed 122 patients with borderline-resectable pancreatic adenocarcinoma who had restaging of their disease after neoadjuvant treatment. Even though only

Table 2. Neoadjuvant therapy trials in pancreatic adenocarcinoma.

Author/year	Location	Resectability (n)	Neoadjuvant therapy	Resection rate	Median OS unresected	Median OS resected
Prospective studies						
Weese JL 1990 [33]	Head (14), Body (1)	R = 15	5-FU + Mitomycin-C + EBRT	ORR = 60% R0 = 60%	7 month	NR
Coia LR 1994 [34]	Pancreatic head/body (27) *Duodenum (4)*	R = 10 UR = 21 (all panc)	5-FU + Mitomycin-C + EBRT	ORR = 55% (48% panc) R0 = 49%	Pancreatic cancer only 15% 1-year	Pancreatic cancer only 60% 1-year
Hoffman JP 1995 [17]	Head/body/tail adenosquamous included	R = 21 UR = 13	5-FU + Mitomycin-C + EBRT	ORR = 32% R0 = 29%	NS	45 month
Kamthan AG 1997 [35]	Head/body/tail	UR = 35	5-FU + Streptozocin + Cisplatin + EBRT → 5FU/leucovorin	ORR = 15% R0 = NS	All patients = 15 month	31 month
Hoffman JP 1998 [36]	Head/body/tail	R = 53	5-FU + Mitomycin-C + EBRT	ORR – 45% R0 – 32%	No surg – 5 month, Surg and no resection – 8 month	15 month
Staley CA 1996 [37]	Head	R = 39	5-FU + EBRT	ORR = 100% R0 = 82%	NA	19 month
Pisters PW 1998 [38]	Head	R = 35	5-FU + rapid fractionation EBRT. Additional intraop RT only if PD	ORR = 57% R0 = 51%	7 month	25 month
Bajetta E 1999 [39]	Head/body/tail	UR = 32	5-deoxyfluridine/leucovorin + EBRT	ORR = 16% R0 = 16%	All patients = 9 month	NS
Snady H 2000 [40]	Head/body/tail	UR = 68	5-FU + Streptozocin + Cisplatin + EBRT	ORR = 29% R0 = 28%	21 month	32 month
Wanebo HJ 2000 [41]	Head/body	R = 5 UR = 6 Unk = 3	5FU + Cisplatin + EBRT	ORR = 64% R0 = 64%	9 month	19 month
Pipas JM 2001 [42]	Head/body/tail	UR = 21	Gemcitabine + EBRT (Phase I study)	ORR = 24% R0 = 24%	NS	NS
Wolff RA 2001 [43]	Head	UR = 18	Gemcitabine + EBRT (Phase I study)	ORR = 5% R0 = 5%	All patients = 6 month	NS
De Lange SM 2002 [44]	Head/body/tail	UR = 24	Gemcitabine + EBRT → Gemcitabine	ORR = 4% R0 = 4%	All patients = 10 month	NS
Epelbaum R 2002 [45]	Head/body/tail	UR = 20	Gemcitabine → Gemcitabine + EBRT	ORR = 15% R0 = 10%	All patients = 8 month	24 month
Pisters PW 2002 [46]	Head/uncinate process	R = 35	Paclitaxel + EBRT Additional intraop RT only if PD	ORR = 57% R0 = 40%	All patients = 12 month	19 month
Al-Sukhun S 2003 [47]	Head/body/tail	UR = 20	Cisplatin + 5-FU + Cytarabine → Caffeine → 5-FU + EBRT	ORR = 15% R0 = NS R1 = NS	All patients = 13 month	24 month

Table 2. Continued.

Author/year	Location	Resectability (n)	Neoadjuvant therapy	Resection rate	Median OS unresected	Median OS resected
Brunner TB 2003 [48]	Head/body/tail	UR = 30	Cisplatin + Gemcitabine + EBRT	ORR = 31% R0 = 28%	11 month	18 month
Joensuu 2004 [49]	Head/body/tail	R = 28	Gemcitabine + EBRT	ORR = 71% R0 = 71%	NS	NS
Moutardier V 2004 [50]	Head/body	R = 61	5-FU + Cisplatin + EBRT	ORR = 65% R0 = 60%	All patients = 13 month UR = 8.6 month	26.6 month
Magnino A 2005 [51]	Head/body/tail	UR = 23	Gemcitabine + EBRT	ORR = 26% R0 = 22%	All patients = 14 month UR = 12 month	20 month
Pipas JM 2005 [52]	Head/body	R = 4 BR = 7 UR = 13	Docetaxel + Gemcitabine → Gemcitabine + EBRT	ORR = 71% R0 = 54%	All patients = 14 month	NS
Mornex F 2006 [53]	Head/body/tail	R = 41	5-FU + Cisplatin + EBRT	ORR = 63% R0 = 51%	All patients = 9.4 month	11.7 month
Talamonti MS 2006 [54]	Head/body/tail	R = 20	Gemcitabine → Gemcitabine + EBRT	ORR = 85% R0 = 80%	All patients = 18 month	26 month
Wilkowski R 2006 [55]	Head/body/tail	UR = 32	Gemcitabine + 5-FU + EBRT → Gemcitabine + Cisplatin	ORR = 18% R0 = 12%	All patients = 13.6 month	16.4 month
Desai SP 2007 [56]	Head/body/tail/mets	R = 12 UR = 29 *metastatic = 3	Gemcitabine + Oxaliplatin + EBRT	ORR = 16% R0 = 16%	UR/metastatic = 9.1 month	20.8 month
Palmer DH 2007 [57]	Head of pancreas by radiology Sp resection 3 pts had malignancy other than pancreatic adenoca	R = 50	Randomized phase II study: (A)Gemcitabine (N = 24) (B)Gemcitabine + Cisplatin (N = 26)	ORR = 38% in A and 70% in B R0 = 75% in both	All patients (A) = 9.9 month, (B) = 15.6 month	28.4 month
Evans DB 2008 [19]	Head/uncinate process	R = 86	Gemcitabine + EBRT	ORR = 74% R0 = 66%	All patients = 22.7 month UR = 7 month	34 month
Heinrich S 2008 [58]	Head	R = 28	Gemcitabine + Cisplatin	ORR = 86% R0/R1 = NS	NS	26.5 month
Le Scodan 2008 [59]	Head/body/tail	R = 41	5-FU + Cisplatin + EBRT	ORR = 63% R0 = 51%	All patients = 9.4 month	11.7 month
Marti JL 2008 [60]	Head/body/tail	UR = 23 BR = 3	Gemcitabine + Cisplatin (n = 26) → Gemcitabine + Cisplatin + EBRT (n = 18)	ORR = 15% R0 = 12%	All patients = 13 month	17 month
Small W 2008 [61]	Head/body/tail	R = 16 BR = 9 UR = 14	Gemcitabine + EBRT	ORR = 81% for R, 33% for BR, 7% for UR	All patients 1-year 73%	NS
Varadhachary GR 2008 [20]	Head/uncinate	R = 90	Gemcitabine + Cisplatin → Gemcitabine + EBRT	ORR = 58% R0 = 56%	All patients 17.4 month, UR 10 month	31 month

Table 2. Continued.

Author/year	Location	Resectability (n)	Neoadjuvant therapy	Resection rate	Median OS unresected	Median OS resected
Bjerregaard JK 2009 [62]	Head/body/tail	UR = 63	UFT + folinic acid + EBRT	ORR = 17% R0 = 17%	8.8 month	46 month
Choi M 2010 [63]	Head/body/tail	UR = 20	Cisplatin + Cytarabine + Caffeine + 5-FU → 5-FU + EBRT	ORR = 15% R0 = NS	All patients = 13.7 month	24.3 month
Laurent S 2009 [64]	Head/body/tail *also had biliary cancer but outcomes separated	UR = 17	Gemcitabine + Oxaliplatin → Gemcitabine + Oxaliplatin + EBRT	ORR = 17% R0 = 17%	All patients = 17 month	NS
Maximous DW 2009 [65]	Head/body/tail	R = 25	Gemcitabine + EBRT	ORR = 32% R0 = NS	All patients = 12 month Unresected 1-year = 22%	1-year = 87%
Turrini O 2010 [66]	Head/body/tail	R = 34	Docetaxel + EBRT	ORR = 50% R0 = 50%	All patients = 15.5 month, unresected 11 month	32 month
Landry J 2010 [67]	Head/body/tail 4 with "other" histology	R = 10 UR = 8 ? = 3	Randomized phase II: [A] Gemcitabine + EBRT (n = 10) [B] Gemcitabine + Cisplatin + 5-FU → 5-FU + EBRT (n = 11). All patients got adjuvant Gemcitabine	ORR, A = 30%, B = 18%	All patients, arm A = 19.4 month, arm B = 14.2 month	22 month in both A and B
Sahora K 2010 [68]	Head/body/tail	UR = 18 BR = 15	Gemcitabine + Oxaliplatin	ORR = 39% R0 = 27% R1 = 9%	12 month	22 month
Lee JL 2012 [69]	Head/body/tail	BR = 18 UR = 25	Dose Dense Gemcitabine + Capecitabine	PR = 18.6% SD = 69.8% R0 = 82% out of 17 resected R1 = 18%	13.1 month	23.1 month
Pipas JM 2012 [70]	Head/body/tail	R = 4 BR = 23 UR = 6	Cetuximab load then Cetuximab + Gemcitabine + EBRT	ORR = 91% (PR = 30%) R0 = 92% out of 70% resected	10 month	24.3 month
Satoi S 2012 [71]	Head/body/tail	R = 23 BR/UR = 7	S1 + EBRT	ORR = 88% (PR = 18%) R0 = 93%	NS	NS
Chao YJ 2014 [72]	Head/body/tail	UR=41	Gemcitabine+5FU+Oxaliplatin+Thalidomide or Gemcitabine+5FU+Oxaliplatin+Sunitinib or Gemcitabine-based Chemoradiation	RR=51.2% (CR=5%, PR=46%)R0 = 31%, R1 = 5%, R2 = 2%	9 month	21 month
Golcher H 2014 [73]	Head	R = 73	Primary surgery or Gemcitabine + Cisplatin + EBRT	4 PR, 8 SD in treatment group R0 = 48 and 52%	NR	18.9 versus 25 month

Table 2. Continued.

Author/year	Location	Resectability (n)	Neoadjuvant therapy	Resection rate	Median OS unresected	Median OS resected
O'Reilly EM 2014 [21]	Head/body/tail	R = 38	Gemcitabine + Oxaliplatin	PR = 10.5% SD = 73.7% R0/R1 = 77%	27.2 month (all)	NS
Retrospective studies						
White RR 2001 [74]	Pancreatic head/body/tail	R = 53, BR or UR = 58	5-FU-based chemotherapy + EBRT [5FU alone (n = 71), w mitomycin (n = 17), with cisplatin (n = 4), combination of 5Fu/mito/cis (n = 13), oral 5FU (n = 6)]	53% in R group, 19% in BR or UR	NS	Actuarial 2 year OS 32%
Aristu J 2003 [75]	head/body/tail,	UR = 49	Chemotherapy + EBRT (one of 3 chemo): Cisplatin + 5FU Cisplatin + 5FU +/− Paclitaxel Gemcitabine + Docetaxel. (23 UR pts got additional EBRT)	ORR = 19%	10 month	22 month
Calvo FA 2004 [76]	Head/body	R = 15	Tegafur + EBRT	ORR = 60% R0 = 46% overall	8 month (UR) 17 month (all)	23 month
Sa Cunha 2005 [77]	Head/body/tail	UR = 61	5-FU + Cisplatin + EBRT	ORR = 21%	11 month (nonresponders)	28 month
Brown KM 2008 [78]	Head/body/tail	BR = 13	Chemo + EBRT (chemo): 5FU (*n* = 3), Gemcitabine (*n* = 9), Capecitabine + Bevacizumab (*n* = 1)	ORR-100% R0 = 85%	NS	NS
Allendorf JD 2008 [79]	Head/body/tail	UR = 78 (preop CRT) versus R = 167 (upfront resection)	Gem + Taxotere + Xeloda (81% of pts) 75% pts also got EBRT	ORR = 76% R0 = 84.7% of resected	16.6 month upfront resection	17.7 month resected sp CRT
Golcher H 2008 [80]	Head/body	UR = 121 (preop CRT) versus R = 58 (upfront resection)	(5FU + Mitomycin) or (Gemcitabine + Cisplatin) + EBRT	ORR = 17% R0 = 90% of 17%	21 month upfront resection	54 month resected sp CRT
Turrini O 2009 [81]	Head	BR = 49, UR = 15	5-FU + Cisplatin + EBRT	ORR = 14%	13 month (UR), 14 month (all)	24 month
Stokes JB 2011 [82]	Head/body/tail	BR = 34	Capecitabine + EBRT	ORR = 46% R0 = 75% of 46%	NS	23 month
Patel M 2011 [83]	Head/body/tail	BR = 17	Gemcitabine + Taxotere + Capecitabine → 5-FU + IMRT	ORR = 53% R0 = 89% of 53%	15.6 month (all)	NS
Arvold ND 2012 [22]	Head/body/tail	BR = 24 UR = 46	5FU or Capecitabine + EBRT	PR = 30% R0 = 79% of 20%	13.2 mo	19.4 month

Table 2. Continued.

Author/year	Location	Resectability (n)	Neoadjuvant therapy	Resection rate	Median OS unresected	Median OS resected
Sho M 2012 [84]	NR	R = 61 BR = 71	Gemcitabine + EBRT	R0 92% versus 52% controls	28 month (neoadjuvant)	NS
Strobel O 2012 [23]	Head/body/tail	R = 120 UR = 137	(5FU, Gemcitabine, or Cetuximab-based) Chemoradiation or Chemotherapy	R0 35%, R1 50.8%, R2 13.3% of 46.7% resected	9 month	13 month
Boone BA 2013 [25]	Head/body/tail	BR = 12 UR = 13	FOLFIRINOX + EBRT	R0 = 33%	NS	NS
Faris JE 2013 [26]	Head/uncinated/tail	UR = 22	FOLFIRINOX +/− 5FU or Capecitabine + EBRT	PR = 27.3% SD = 72.7% R0 = 23%	NS	NS
Papavasiliou P 2014 [24]	Head/uncinate	NS	Gemcitabine or 5FU + EBRT	RR = NS R0 = 68.5%, R1 = 30.6%, R2 = 0.9%	22 month (all)	NS
Rose JB 2014 [32]	Head/body/tail	BR = 64	Gemcitabine + Docetaxel	R0 = 87% of 61%	15.4 month 23.6 month (all)	NR

R, resectable; BR, borderline resectable; UR, unresectable; UNK, unknown; ORR, overall resection rate; R0, complete microscopically negative; R1, positive margin; PD, pancreaticoduodenectomy; EBRT, external beam radiotherapy; OS, overall survival; NS, not specified; NR, not reached; NA, not applicable; 5-FU, 5-Fluorouracil; FOLFIRINOX, Folinic acid, 5-Fluorouracil, Irinotecan, Oxaliplatin; C, cycle; →, followed by.

12% of patients met the RECIST imaging criteria for a partial response and only one patient (0.8%) was officially downstaged to resectable, (69% had stable disease and 19% had progressive disease), 66% of the patients were able to undergo pancreaticoduodenectomy. Median OS for patients who underwent surgery was 33 versus 12 months for those who did not.

In an attempt to determine aggregate outcome measures; Gillen et al. performed a systematic review on neoadjuvant therapy trials in pancreatic cancer [27]. This meta-analysis looked at more than 100 neoadjuvant trials published since 1980, despite the heterogeneity of patients enrolled and regimens used. Of those patients considered resectable at diagnosis, approximately 74% went on to have surgical resection after neoadjuvant treatment with an R0 resection rate of 82%. Median survival in this group was 23.3 months (range 12–54 months) with 2-year survival of 47%. These survival results are comparable to patients who had initial surgery first followed by adjuvant therapy. Among the patients that were deemed to be initially unresectable, the overall resection rate after neoadjuvant treatment was 33% with R0 resection rate of 79%. The median OS was 20.5 months (range 9–62 months) with a 2-year survival of 50% for this group. Median survival, however, was only 10.2 months for those patients whose disease remained unresectable despite neoadjuvant treatment, which is similar to patients who were treated with palliative intentions (median survival 8–12 months). Despite the data, no standard regimen or sequence of treatment could be conclusively determined.

Further adding to the published data on this topic, Artinyan and colleagues conducted a population-based cohort series [28]. Using the California Cancer Surveillance Program, 458 patients with pancreatic adenocarcinoma who underwent surgical resection and received systemic chemotherapy between 1987 and 2006 were retrospectively analyzed. Neoadjuvant treatment was delivered in about 9% of the patients and adjuvant treatment given in 91% cases. Patient characteristics such as age, gender, and tumor size were similar between the two groups; however, data on performance status or co-morbidities were not reported. There was a significantly lower rate of positive pathologic lymph nodes in the neoadjuvant group (45% vs. 65%) despite a higher rate of extra-pancreatic tumor extension. The neoadjuvant group also had significantly better OS compared with the adjuvant group (median survival, 34 vs. 19 months). While there are obvious limitations of a population-based cohort study, it is clear that only a small percentage of patients in that clinical practice environment received neoadjuvant treatment. Thus, such patients are likely highly selected individuals.

Nonetheless, this summative data combined with the systematic review and meta-analyses suggest that neoadjuvant therapy can be conducted safely in select patients and may possibly benefit a subset of those with resectable and borderline-resectable disease. By introducing early systemic treatment to combat distant relapses coupled with avoidance of a radical surgical resection in patients whose disease is biologically aggressive, neoadjuvant treatment offers many advantages. However, the magnitude of

Table 3. Outcomes of selected randomized controlled clinical trials in metastatic pancreatic adenocarcinoma.

Reference	Treatment	Total *N*	Median survival (month)	*P*-value
Bramhall SR, BJC 2002 [85]	Gemcitabine +/– Marimastat	239	5.4 versus 5.5	0.95
Berlin JD, JCO 2002 [86]	Gemcitabine +/– 5-FU	322	5.7 versus 6.5	0.09
Colucci G, Cancer 2002 [87]	Gem versus Gem + Cisplatin	107	5 versus 7.5	0.43
Rocha Lima CM, JCO 2004 [88]	Gemcitabine +/– Irinotecan	342	6.3 versus 6.6	0.78
Van Custem E, JCO 2004 [89]	Gemcitabine +/– Tipifarnib	688	6.1 versus 6.4	0.75
Louvet C, JCO 2005 [90]	Gemcitabine +/– Oxaliplatin	313	7.1 versus 9	0.13
Oettle H, Ann Oncol 2005 [91]	Gemcitabine +/– Premetexed	565	6.3 versus 6.2	0.84
Abou-Alfa GK, JCO 2006 [92]	Gemcitabine +/– Exatecan	349	6.2 versus 6.7	0.52
Heinemann V, JCO 2006 [93]	Gem versus Gem+Cisplatin	195	6 versus 7	0.15
Stathopoulous GP, BJC 2006 [94]	Gemcitabine +/– Irinotecan	145	6.4 versus 6.5	0.97
Herrmann R, JCO 2007 [95]	Gemcitabine +/– Capecitabine	319	7.2 versus 8.4	0.23
Moore MJ, JCO 2007 [96]	Gemcitabine +/– Erlotinib	569	5.9 versus 6.3	**0.03**
Poplin E, JCO 2009 [97]	Gemcitabine versus fixed dose rate	832	4.9 versus 6 versus 5.7	**0.04**
	Gemcitabine versus Gemcitabine + Oxaliplatin			0.22
Van Custem E, JCO 2009 [98]	Gemcitabine+Erlotinib +/– Bevacizumab	301	6.0 versus 7.1	0.20
Kindler HL, JCO 2010 [99]	Gemcitabine +/– Bevacizumab	602	5.9 versus 5.8	0.95
Philip PA, JCO 2010 [100]	Gemcitabine +/– Cetuximab	745	5.9 versus 6.3	0.23
Conroy T, NEJM 2011 [24]	Gemcitabine versus FOLFIRINOX	342	6.8 versus 11.1	**<0.001**
Von Hoff, NEJM 2013 [101]	Gemcitabine +/– nab-paclitaxel	861	8.5 versus 6.7	***P* < 0.001**

5-FU, 5-fluorouracil; +/–, one arm with and one arm without the drug following the sign.
Bold indicates statistically significant.

the impact has yet to be demonstrated or validated in a randomized controlled trial.

Final Thoughts

Despite the opportunity to improve survival by incorporating systemic treatment in the neoadjuvant setting and better selection of patients with truly localized cancer, survival in this dreaded disease still remains modest. The key to significantly impacting survival, short of prevention, would be the identification of therapeutic interventions tailored to the patient, which can overcome the inherent resistance mechanisms evoked by the cancer. To achieve this goal of appropriate patient selection based on patient and disease characteristics and to optimize their chance of receiving the optimal medical, radiation and surgical treatment, a multidisciplinary, collaborative approach to the care of each and every patient with pancreatic adenocarcinoma is imperative. Despite all the strides in various oncologic disciplines the ability to offer a cure to most patients remains unachievable. Perhaps the best case for neoadjuvant multidisciplinary approach is to rapidly test novel hypotheses and the effects of various treatments on the tumor and the surrounding microenvironment. A neoadjuvant platform could gain insights into the tumor biology, which may ultimately hold the key to achieving cure for most, if not all patients afflicted with this deadly disease. However, this requires adequate tissue acquisition of the tumor tissue to confirm the initial diagnosis. Increased cytologic yield through endoscopically obtained core biopsies or circulating tumor cells will be required in the future to fully realize the molecular characterization and personalized therapeutics potential.

The less than ideal response to cytotoxic and targeted therapies is evident in the abundant trials in the metastatic setting that have consistently failed to demonstrate a statistically significant or clinically meaningful advantage over single agent gemcitabine (Table 3). Only recently have FOLFIRINOX and gemcitabine with nab-paclitaxel raised the bar [29–31]. While the use of two or three cytotoxic drugs showed significant survival advantage over gemcitabine alone (median OS 11.1 vs. 6.8 months; $P < 0.001$) in patients with metastatic disease, toxicities limit use to select patients with excellent performance status and no major comorbidities.

Thus, the future of effective pancreatic cancer therapy must take into consideration not just the cancer, but also the interplay of the tumor microenvironment, the inherent biologic features that confer early metastatic potential to the cancer, the role of cancer stem cells in therapy resistance mechanisms, and novel gain of function mutations that may serve as new targets for therapeutic disruption. Only an adequately powered prospective study will be able to determine if neoadjuvant therapy provides a survival advantage for early stage pancreatic cancer patients. This study should randomize patients with borderline-resectable disease to the most effective systemic chemotherapy and/or chemoradiotherapy before or after surgery, and explore important outcomes such as relapse free survival and OS. Secondary end points should include resection rates, toxicity and surgical complications. At this moment, however, no such trial exists and neoadjuvant therapy should be conducted as part of an investigational program.

Conflict of Interest

None declared.

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