Past, Present, and Future of Neoadjuvant Therapy for Pancreatic Cancer

Author:

Alexander V. Fisher[1]

Brian S. Chu[2]

Daniel E. Abbott[1]

Affiliations:

[1] University of Wisconsin, Department of Surgery, United States

[2] University of Cincinnati, College of Medicine, United States

Correspondence author:

Daniel E. Abbott[1]

E-mail: abbott@surgery.wisc.edu

Abstract

Pancreatic cancer is a leading cause of cancer death with overall 5-year survival of 5%. For the small proportion of patients who present with localized disease, surgical resection remains a necessary treatment component to achieve lasting survival. Over the past 20-30 years, multi-modal therapy involving the addition of chemotherapy and/or radiation has emerged as an important adjunct to surgery in order to prolong survival. However, patients undergoing resection are often affected by surgical complications, early recurrences, and inability to receive the recommended adjuvant therapy. For these reasons, neoadjuvant therapy has emerged as an attractive option, and in the United States, there has been a significant trend towards neoadjuvant treatment for resectable and borderline-resectable pancreatic tumors. In this review, historical evidence leading to the emergence of neoadjuvant treatment and recent studies of neoadjuvant regimens are summarized. Finally, an overview of ongoing randomized clinical trials is presented.

Keywords: Pancreatic Cancer, Neoadjuvant Therapy, Chemotherapy, Chemoradiation

1. Introduction

Pancreatic cancer is the third leading cause of cancer death in the United States.[1] The prevalence of this deadly disease is rising, and mortality estimates suggest it will surpass colon cancer to become the 2nd leading cause of cancer death by 2030.[2] Approximately 80% of patients with pancreatic ductal adenocarcinoma (PDAC) present with metastatic disease at time of diagnosis, and even with modern chemotherapy regimens, median survival is limited to 8-11 months.[3,4] Meanwhile, the remaining 20% of patients will have locoregional disease which is potentially amenable to resection, and can be classified according to National Comprehensive Cancer Network (NCCN) guidelines as being 1) resectable 2) borderline-resectable, or 3) locally advanced, unresectable.[5] These staging criteria are based on the tumoral-vasculature relationship and determine the feasibility of complete tumor removal, with or without vascular reconstruction.

Chemotherapy remains the mainstay of treatment for patients with metastatic or locally advanced disease, while radiation therapy is sometimes utilized to prevent or alleviate symptoms in patients who are not candidates for a curative-intent resection. Treatment options for patients with resectable and borderline resectable disease ideally consists of multimodal therapy which should include some combination of surgery, chemotherapy, and radiation therapy; this multimodal approach can significantly impact long-term survival outcomes.[6] With multimodal therapy, five-year survival for patients undergoing resection can be as high as 27%.[6] However, the ideal combination and sequence of multimodal treatment delivery, i.e. surgery followed by adjuvant therapy versus neoadjuvant therapy followed by surgery, has remained a heated topic of debate in the oncologic and surgical communities.

Randomized trials comparing neoadjuvant versus adjuvant treatment strategies for patients with resectable or borderline resectable PDAC are lacking, and this has led to wide variation in practice patterns and opinions about the optimal timing of surgery. However, there has been a national trend towards increased utilization of neoadjuvant therapy for patients with resectable disease,[7] and in fact the surgery-first approach in borderline resectable disease is no longer endorsed.[5] This review summarizes the history of neoadjuvant therapy for pancreatic cancer, reviews major landmark studies pertaining to adjuvant and neoadjuvant therapy, and summarizes ongoing clinical trial that will provide future direction.

2. Neoadjuvant Treatment Considerations

Proponents of neoadjuvant therapy for pancreatic ductal adenocarcinoma argue many benefits for early delivery of systemic chemotherapy and/or locoregional chemoradiation therapy. Due to the aggressive nature of pancreatic ductal adenocarcinoma, even patients with resectable disease are believed to likely harbor radiographically occult metastatic disease (micrometastases). This is evidenced by patients undergoing curative-intent resection demonstrating very high rates of disease recurrence with an associated 5-year survival under 20%.[8,9] Additionally, delaying surgery for 3-6 months allows time for restaging prior to surgery, at which time biologically aggressive disease may declare itself in the form of newly discovered metastases in liver, lung or other sites. For patients with initially resectable tumors, disease progression and/or metastases while receiving neoadjuvant therapy is believed to

occur in 15-20% of patients, with the remaining 80-85% proceeding to pancreatic resection.[10,11] While there is no direct evidence that patients experiencing disease progression would not have benefited from early surgery, it is generally argued that selecting out the subset of patients who experience disease progression while on neoadjuvant treatment protocols can eliminate futile, major surgery. These patients can be spared the morbidity of major pancreatectomy that would have likely conferred little to no survival benefit, and additionally results in a more cost-effective treatment approach.[12]

Margin status following resection is an important feature of high-quality surgical care. R0 resections are associated with improved survival, with some data demonstrating that an R1 resection is associated with similar outcomes when compared to patients treated with chemotherapy and radiation without surgery.[8,13,14] For these reasons, achieving an R0 resection is the primary goal for surgeons, and efforts to increase the likelihood of R0 resection is of the utmost importance. Neoadjuvant therapy has been shown to increase the likelihood of achieving a margin-negative resection, especially for patients with borderline resectable disease, where >90% R0 resection rates can be observed when neoadjuvant therapy is delivered.[8,13,15,16] Furthermore, for patients who initially present with locally-advanced unresectable tumors, up to 1 in 4 may be converted to resectable disease following neoadjuvant treatment, and of those resected, R0 resections can occur in >80%.[15]

An added benefit of the neoadjuvant approach is the high rate of completion of multi-modality therapy. It is well described that approximately 30% of patients do not go on to receive chemotherapy after pancreatic resection, and thus a chemotherapy-first approach ensures patients get systemic therapy for what is likely a systemic disease.[17,18] Additionally, surgical alteration of blood flow and oxygen delivery to the residual tumor bed may decrease the effectiveness of radiation and chemotherapy when delivered in the adjuvant setting.

For patients with resectable disease, the primary argument put forth by proponents of a surgery-first approach is that surgery offers the only chance for long-term survival and possible cure. Delaying a potentially curative treatment may risk disease progression, thus losing the window of opportunity in which surgical intervention is possible; some early studies found that up to 50% of patients never went on to pancreatic resection, despite initially presenting with resectable tumors.[19,20] However, a 2010 meta-analysis by Gillen et al. showed 73.6% of patients with resectable disease were able to undergo resection after completing neoadjuvant treatment.[21] Furthermore, without clear evidence of systemic disease, the toxic side effects of chemotherapy may lead to patient preference for choosing upfront surgery. Finally, when attempts to obtain a definitive tissue diagnosis fail, a surgery-first approach is appropriate in the setting of high clinical suspicion for pancreatic cancer.

3. History of Multi-modal Therapy

The emergence of neoadjuvant therapy for pancreatic cancer occurred out of both necessity and opportunity, tracing back to the emergence of adjuvant therapy. Indeed, many lessons learned from adjuvant studies have been extrapolated into the neoadjuvant setting, and only very recently have large randomized trials examining neoadjuvant therapy emerged. Potentially curative surgical resection has long been the standard treatment for localized pancreatic cancer.[22] However, 85% of resected patients ultimately develop metastases or local recurrence within 9-15 months, with median

life expectancy of only 12-15 months.[23] The necessity for better treatment spurred investigational studies beginning in the 1980's into multi-modal therapy with adjuvant chemoradiotherapy and chemotherapy based on 5-fluorouracil (5-FU).[24,25] A pivotal early study of adjuvant therapy was the Gastrointestinal Tumor Study Group (GITSG) trial, which demonstrated significantly improved median survival (20 months vs. 11 months) and improved 2-year survival (43% vs. 18%) in patients who received adjuvant chemoradiotherapy followed by maintenance 5-FU chemotherapy (compared to those randomized to surgery alone).[24] Adjuvant therapy soon became universally recommended for patients with resected pancreatic cancer. A summary of randomized trials of adjuvant therapy trials provided in Table 1.

Table 1: Randomized Trials of Adjuvant Therapy for Resected Pancreatic Cancer

Reference	Margin	n	Adjuvant Therapeutic Comparison	Survival (mo) Arm 1 vs 2	Comments
GITSG[24,25] 1985, 1987	R0	49	Arm 1: CRT (5-FU, 40 Gy) Arm 2: Observation	20 vs. 11 p=0.035	Study terminated prematurely.
Bakkevold et al.[26] 1993	R0	61 (47 PC)	Arm 1: CT (AMF) Arm 2: Observation	23 vs. 11 p=0.02	PC and Ampullary Ca.
EORTC[27] 1999	R0+R1	218 (114 PC)	Arm 1: CRT (5-FU, 40 Gy) Arm 2: Observation	24.5 vs. 19.0 p=0.208	Included Ampullary Ca. For PC only, survival 17 vs. 13 months (p=0.099)
ESPAC-1[28] 2004	R0+R1	289	Arm 1: CRT (5-FU, 20 Gy) Arm 2: CT (5-FU) Arm 3: CRT + CT Arm 4: Observation	20.1 (Arm2/3) vs 15.5 (Arm 1/4) p=0.009	CRT conferred worse survival.
CONKO-001[29,30] 2007, 2013	R0+R1	368	Arm 1: CT (Gemcitabine) Arm 2: Observation	22.8 vs 20.2 p=0.01	
RTOG 97-04.[31] 2008	R0+R1	451	Arm 1: CT (5-FU)+ CRT (5-FU, 50.4 Gy) Arm 2: CT (Gem) + CRT (5-FU, 50.4 Gy)	16.9 vs 20.5 p=0.09	Arm 2 showed survival benefit (p=0.05) on MVA.
Van Laethem et al.[32] 2010	R0+R1	90	Arm 1: CT (Gem) Arm 2: CT (Gem) + CRT (Gem, 50.4 Gy)	24.4 vs 24.3	Fewer local recurrence in CRT group (11% vs 24%)
Schmidt et al.[33] 2012	R0+R1	132	Arm 1: CRT (5-FU, cisplatin, IFN, 50.4 Gy) + CT (5-FU) Arm 2: CT (5-FU)	26.5 vs 28.5 p=0.99	85% Grade 3/4 toxicity in Arm 1.

PC: Pancreatic Cancer. CT: Chemotherapy. CRT: Chemoradiotherapy Gem: Gemcitabine. 5-FU: 5-fluorouracil. AMF: Adriamycin, mitomycin C, 5-fluorouracil. IFN: Interferon α-2b. Ca: Cancer. MVA: Multivariate analysis.

At the same time, the notion of neoadjuvant therapy emerged as many patients who underwent curative resection failed to receive postoperative adjuvant therapy due to complications, delayed recovery or failure to return to an adequate baseline.[17,18] Early trials of neoadjuvant therapy were largely carried out in patients with locally advanced pancreatic cancer (LAPC). In one of the first studies of neoadjuvant therapy for pancreatic cancer, Pilepich et al. demonstrated that radiation therapy was effective in converting six of seventeen patients from unresectable to resectable disease status.[34] Later, Jessup et al. utilized a neoadjuvant regimen of 5-FU based chemoradiation in sixteen unresectable patients and ultimately found conversion to resectable disease in two.[35]. More promising results were seen in a study by Hoffman et al., where the authors reported that 11 of 34 patients with LAPC were able to undergo potentially curative resection after treatment with chemoradiotherapy.[36] As the potential benefit of neoadjuvant therapy became apparent, further investigation of neoadjuvant and adjuvant regimens continued throughout 1990-2000, and mainly consisted of chemotherapy with 5-fluorouracil with or without concomitant chemoradiotherapy.[37]

Multiple GITSG studies investigated the use of different combinations of chemotherapeutic agents such as 5-FU, doxorubicin, streptozocin and mitomycin-C without any significant differences in overall survival.[38,39] Thus, 5-FU remained the backbone chemotherapeutic for all stages of pancreatic cancer for many years until the late 2000's, and data supporting its use in the adjuvant setting were extended for use in select patients receiving neoadjuvant treatment.[40,41] However, neoadjuvant therapy in this era commonly consisted of chemoradiation alone, without delivery of any systemic treatments. [19,40–43]

To address the role of locoregional chemoradiation versus full-dose chemotherapy targeting systemic disease, The European Study Group for Pancreatic Cancer-1 trial (ESPAC-1) sought to evaluate adjuvant treatment strategies with 5-FU chemotherapy versus chemoradiation to 20-Gy in patients who completed curative-intent pancreatic resection. By using a 2x2 factorial design consisting of 4 arms, investigators found that the groups receiving chemotherapy alone or chemotherapy and chemoradiation had a significant survival benefit compared to the combined groups receiving chemoradiation alone and observation alone (5-year survival 21% vs 8%).[28] Analysis of the two arms receiving chemoradiation showed 5-year survival of only 10%, compared to 20% in the two arms not receiving chemoradiation. The authors concluded that chemoradiation was harmful in the adjuvant setting and that chemotherapy alone was responsible for imparting a survival benefit, possibly because chemoradiation occurred soon after surgery, thereby causing a delay in the initiation of chemotherapy. Unfortunately, the trial was not powered to detect a survival difference between individual arms of the study, however, median survival was longest in those receiving chemotherapy alone at 21.6 months, and was shortest in the chemoradiation arm at 13.9 months.

The ESPAC-1 trial has received a significant amount of criticism around trial design, lack of standardized radiation regimens, and low-dose radiation treatment to only 20-Gy, instead of the traditional 50.4-Gy dosing.[44–48] Due to these criticisms and skepticism surrounding the results, adjuvant chemoradiation is still used in the United States. A subsequent multi-institutional retrospective study has suggested a role for adjuvant radiation in a subset of patient who are lymph-node positive, while another large multi-center study has suggested use of chemotherapy

alone, with no additional benefit derived from adding chemoradiation.[49,50]

Gemcitabine-based therapy began to emerge after promising studies in the 1990's demonstrated acceptable safety and improved efficacy compared to fluorouracil for patients with locally advanced disesase.[51] A decade later, the CONKO-001 trial demonstrated improved disease-free survival for patients who underwent curative-intent resection followed by adjuvant gemcitabine for 6 months compared to observation alone.[29] The final report of the CONKO-001 trial in 2013 also showed prolonged overall 5-year survival of 20.7% in the gemcitabine arm compared to only 10.4% for those receiving surgery followed by observation.[30] The use of gemcitabine in the adjuvant setting was further explored in the RTOG 97-04 phase III trial of 451 patients who were randomized to receive either 3 weeks of gemcitabine or 5-fluorouracil (5-FU) chemotherapy, followed by fluorouracil-based chemoradiation to 50.4 Gy, and finally 12 additional weeks of chemotherapy. Three-year survival was 31% in the gemcitabine arm compared to 22% for fluorouracil. Although not statistically significant for the primary endpoint, multivariable analysis correcting for pre-specified tumor factors showed a survival advantage for gemcitabine with $p=0.05$.[31] Following CONKO-001 and RTOG 97-04, gemcitabine was established as the first-line chemotherapeutic in the adjuvant setting, and again, data from the adjuvant setting was often extrapolated to justify gemcitabine-based neoadjuvant chemotherapy treatment.[52]

Two recent phase III trials in 2011 and 2013 examined new combination chemotherapy regimens in patients with metastatic disease. The PRODIGE Intergroup trial in Europe demonstrated that a regimen of FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) resulted in significantly prolonged median survival at 11.1 months compared to 6.8 months for those receiving gemcitabine alone.[4] Two years later, an additional international multi-center trial demonstrated that the addition of albumin bound paclitaxel (nab-paclitaxel) to a gemcitabine regimen could prolong survival to 8.5 months, compared to 6.7 months for gemcitabine alone.[3] The results from these trials in the metastatic setting have led to FOLFINIROX regimens being increasingly used for neoadjuvant therapy, and indeed, several randomized trials are underway to investigate this further for both resectable and borderline resectable patients.[53]

4.1. Neoadjuvant Chemotherapy Regimens

Currently, no randomized trials have been completed to guide treatment in the neoadjuvant setting. For this reason, chemotherapy treatment decisions are largely extrapolated from adjuvant or metastatic treatment regimens, or from small non-randomized prospective phase II studies. Gemcitabine and fluoropyrimidine based regimens remain the mainstay of treatment options, and are often combined with taxanes or platinum-based agents. The most common fluropyrimidines studied are 5-fluoruracil and capecitabine, the latter having the convenience of being available in oral form. A summary of prospective studies of neoadjuvant therapy are provided in Table 2.

Table 2: Prospective Neoadjvuant Trials for Resectable and Borderline Resectable Pancreatic Cancer

Authors	Resectability	Systemic Therapy	Radiation/Chemoradiation	Outcomes
Randomized Trials				
Palmer et al.,[20] 2007	RPC (n=50)	Arm A: Gem Arm B: Gem + Cis	n/a	-Terminated early by DMC -Arm A: 38% resected, 75% R0, 42% 1-yr OS -Arm B: 70% resected, 75% R0, 62% 1-yr OS
Landry et al.,[54] 2010	BRPC (n=21)	Arm A: n/a Arm B: Gem + Cis + 5-FU	A: Gem-XRT 50.4 Gy B: 5-FU-XRT 50.4 Gy	-Terminated early due to low accrual. -Arm A: 30% resected, 66% R0, 19.4 mo median OS for all pts -Arm B: 18% resected, 50% R0, 13.4 mo median OS for all pts
Golcher et al.,[55] 2015	RPC (n=66)	Arm A: primary surgery Arm B: n/a	Arm A: primary surgery Arm B: Gem-cis-XRT 50.4 Gy	-Terminated early due to low accrual. -Arm A: 70% resected, 70% R0, 18.9 mo median OS for all pts. -Arm B: 58% resected, 89% R0, 25.9 mo median OS for all pts.
Casadei et al.,[56] 2015	RPC (n=38)	Arm A: primary surgery Arm B: Gem	Arm A: primary surgery Arm B: Gem-XRT 45 Gy	-Terminated early due to low accrual. -Arm A: 75% resected, 25% R0, 19.5 mo median OS for all pts. -Arm B: 61% resected, 39% R0, 22.4 mo median OS for all pts.
Non-randomized phase I and II Trials				
Talamonti et al.,[57] 2006	RPC (n=20)	Gem	XRT 36 Gy (concurrent)	-17 (85%) resected, 94% R0 -26 mo. median OS for resected pts.
Mornex et al.,[58] 2006	RPC (n=41)	5-FU + Cis	XRT 50 Gy (concurrent)	-63% resected, 80% R0 -11.7 mo median OS for resected pts
Heinrich et al.[59], 2008	RPC (n=28)	Gem + Cis	n/a	-89% resected, 80% R0 -19.1 mo median OS for resected pts
Evans et al.,[10] 2008	RPC (n=86)	n/a	Gem-XRT 30 Gy	-74% resected, 89% R0 -22.7 mo median OS for all pts, 34 mo median OS for resected pts
Varadhachary et al.,[11] 2008	RPC (n=90)	Gem + Cis	Gem-XRT 30 Gy	-58% resected, 96% R0 -17.4 mo median OS for all pts, 31 mo median OS for resected pts
Turrini et al.,[60] 2010	RPC (n=34)	n/a	Docetaxel-XRT 45 Gy	-50% resected, 100% R0 -32 mo median OS for resected pts
Sahora et al.,[61] 2011	BRPC (n=15) LAPC (n=18)	Gem + Oxaliplatin	n/a	-47% resected for BRPC, 33% for LAPC, 69% overall R0. -22 mo median OS for resected pts
Sahora et al.,[62] 2011	BRPC (n=12) LAPC (n=13)	Gem + Docetaxel	n/a	-33% resected for BRPC, 31% for LAPC, 87% overall R0 -16.3 mo median OS for resected pts
Lee et al.,[63] 2012	BRPC (n=18) LAPC (n=25)	Gem + Capecitbine	n/a	-61% resected for BRPC, 24% for LAPC, 82% overall RO -23.1 mo median OS for resected pts
Pipas et al.,[64] 2012	RPC (n=4) BRPC (n=23) LAPC (n=6)	n/a	Cetuximab-Gem-IMRT 54 Gy	-100% resected for RPC, 78% for BRPC, 50% for LAPC, 92% overall R0 -24.3 mo median OS for resected pts

Kim et al.,[65] 2013	RPC (n=23) BRPC (n=39) LAPC (n=6)	Gem + Oxaliplatin	XRT 30 Gy (concurrent w/ chemo)	-57% resected for RPC, 72% for BRPC, 33% LAPC, 84% overall R0 -21.1 mo median OS for resected pts
Shinoto et al.,[66] 2013	RPC (n=26)	n/a	Carbon-ion radiotherapy 36 Gy (short course)	-81% resected, 90% R0 -18.6 mo median OS for all pts
Tinchon et al.,[67] 2013	BRPC (n=10) MPC (n=2)	FOLFIRINOX	n/a	-83% resected for all pts.
Motoi et al.,[68] 2013	RPC (n=19) BRPC (n=16)	Gemcitabine + S-1	n/a	-86% resected overall, 87% overall R0 -19.7 mo median OS for all pts
Wo et al.,[69] 2014	RPC (n=10)	n/a	Capecitabine-XRT or IMRT to 55 Gy (short course)	Closed-early due to increased intra-operative complications.
Sahora et al.,[70] 2014	BRPC (n=11) LAPC (n=19)	Gem + Bevacizumab	n/a	-37% resected overall -13 mo median OS for all pts
O'Reilly et al.,[71] 2014	RPC (n=38)	Gem + Oxaliplatin	n/a	-71% resected, 74% R0 -27.2 mo median OS for all pts -22 mo median RFS for resected pts
Hong et al.,[72] 2014	RPC (n=50)	n/a	Capecitabine-Proton RT (short-course)	-77% resected, 84% R0 -17.3 mo median OS for all pts -27.0 mo median OS for resected pts
Chan et al.,[73] 2016	RPC (n=1) BRPC (n=12) LAPC (n=8)	n/a	Vorinostat-Capecitabine-XRT 30 Gy	-33% BRPC resected, 75% RO -0% LAPC resected -13 mo median OS for all pts
Masui et al.,[74] 2016	BRPC (n=18)	Gem + S-1	n/a	-83% resected.80% R0 -21.7 mo median OS for all pts
Okada et al.,[75] 2017	BRPC (n=10)	Gem + Nab-Paclitaxel	n/a	-80% resected, 70% R0
Nagakawa et al.,[76] 2017	BRPC (n=27)	Gem + S-1	IMRT 50.4 Gy (concurrent)	-70% resected, 95% R0 -22.4 mo median OS for all pts

RPC: Resectable Pancreatic Cancer. BRPC: Borderline Resectable Pancreatic Cancer. LAPC: Locally-advanced, unresectable pancreatic cancer. Gem: gemcitabine. Cis: cisplatin. 5-FU: 5-fluorouracil. XRT: External Beam Radiation Therapy. IMRT: Intensity-modulated radiation therapy. FOLFIRINOX: Folinic acid, 5-FU, irinotecan, oxaliplatin. DMC: Data monitoring committee. OS: overall survival. R0: margin-negative resection rate (of patients resected). Pts: Patients.

Neoadjuvant gemcitabine monotherapy has been studied in several small phase I and II trials of patients with resectable disease, with acceptable toxicity profiles and high rates of patients proceeding to R0 resection.[77,57,78] Gemcitabine-based therapy has remained common since CONKO-001 and RTOG 97-04 results showed benefit in the adjuvant setting, though certainly it is an evolving paradigm.[30,31] Prior to more recent efficacy data highlighted above, combination gemcitabine regimens with the addition of cisplatin have been studied. Palmer et al. examined a cohort of 50 patients with resectable disease who were randomized to receive gemcitabine or gemcitabine plus cisplatin.[20] Those receiving combination neoadjuvant chemotherapy had a higher rate of proceeding to pancreatic resection (70% vs. 38% for gemcitabine alone), and there were no observed increases in surgical complications, with high rates of R0 resections (75%) in both arms. Combination gemcitabine and cisplatin for patients with resectable disease was further studied by Heinrich and colleagues, with 26 of 28 patients proceeding to pancreatectomy, 80% undergoing R0 resections, and a demonstrated median overall survival of 19.1 months.[59] Partial pathologic response was observed in 53% of patients. Varadhachary et al. reported the MD Anderson experience with neoadjuvant gemcitabine and cisplatin chemotherapy

combined with radiation, and 62 of 90 (69%) patients proceeded to surgery, with 52 undergoing resection. Median survival was 31 months for the group completing multi-modality therapy, compared to 10.5 months for those not proceeding to surgery.[11] Similar results were seen when utilizing gemcitabine-based chemoradiation without chemotherapy, with median survival of 34 months in resected patients.[10]

A variety of other agents including bevacizumab, oxaliplatin, and docetaxel have been added to gemcitabine regimens in phase I/II studies of patients with non-metastatic pancreatic cancer.[79–81] The exact role of these drugs and additional benefit gained in patients with resectable and borderline resectable disease has yet to be fully delineated. Nab-Paclitaxel is another chemotherapeutic of interest in the neoadjuvant setting. Pancreatic ductal adenocarcinomas are known to induce an intense desmoplastic response characterized by dense fibrous tissue surrounding the tumor, which is believed to impede the delivery of chemotherapy to cancer cells. Nab-paclitaxel, in particular, has been shown to disrupt the collagen architecture, which may increase efficacy of concurrent chemotherapy.[82] Safety and feasibility have been examined with neoadjuvant nab-paclitaxel plus gemcitabine in patients with resectable and borderline resectable tumors, thus paving the way for future randomized studies to fully evaluate efficacy of this regimen.[75,83]

Based on trials in patients with stage IV disease, a modified FOLFIRINOX regimen has become a popular treatment choice over gemcitabine for patients receiving neoadjuvant therapy, especially those with borderline resectable disease or locally advanced disease.[15,53,84] A 2015 meta-analysis examined thirteen studies encompassing 253 patients with BRPC or LAPC who received FOLFIRINOX with or without radiation. 43% of patients underwent resection following FOLRININOX treatment and restaging, and the R0 resection rate was 85%.[15] One year later, a retrospective study by Hackert et al. reported a significantly higher resection rate of 60% in a cohort with LAPC treated with FOLFIRINOX, compared to 46% resection rate after gemcitabine, and 52% following other treatment regimens.[85] However, this higher resection rate did not correlate to any significant differences in median overall survival between the three groups (16.0 vs. 16.5 vs. 14.5 months, respectively). Kim et al. reported data on 22 patients undergoing FOLFIRINOX alone without radiation therapy and showed promising results with 91% R0 resection rate and disease-free survival of 22.6 months, calling into question the need for neoadjuvant radiotherapy when FOLFIRINOX is used.[86] The apparent efficacy of FOLFIRINOX for LAPC and BRPC is encouraging, and its role in neoadjuvant therapy will likely continue to expand.

4.2. Neoadjuvant Radiation Therapy Regimens

Radiotherapy (RT) alone is rarely used for treatment of pancreatic cancer given high rates of failure and local progression in up to 80% of cases.[87] RT has been supplanted by chemoradiotherapy (CRT), which most often refers to the practice of using small radio-sensitizing doses of chemotherapy before or during radiation beam delivery. Compared to radiation therapy alone, CRT has demonstrated superior survival and lower toxicity for a variety of malignancies, including pancreatic, esophageal, breast, and head and neck cancer.[25,88–92] The combined experience with CRT in pancreatic and other cancers has led to CRT becoming the most common method for delivery of external beam radiation in patients with pancreatic exocrine tumors in the United States. Several reports in the literature also use the term chemoradiotherapy to refer to RT that is

delivered concurrently with full-dose chemotherapy. For example, studies have reported using gemcitabine-based chemoradiotherapy with gemcitabine doses anywhere from 50 mg/m^2 to 1000 mg/m^2.[10,56,57] While chemoradiotherapy is traditionally conceived as a method to achieve local tumor control, studies utilizing high dose chemotherapy are also contributing to systemic disease treatment. This wide dosing range of chemotherapy used for chemoradiation regimens likely contributes to variable responses and survival outcomes between studies, and thus comparisons should be made cautiously.

The majority of patients with pancreatic cancer will die from metastatic disease, however, approximately 30% of patients die from progression of the primary tumor, thus highlighting the importance of adequate locoregional therapy in the form of CRT and/or surgery.[93] Furthermore, radiation may improve margin-negative resection rates with the belief that this will translate into improved long-term outcomes.[9,14]

Modern radiation therapy (RT) for pancreatic cancer consists of a variety of techniques designed to deliver concentrated radiation to the tumor bed and avoid normal tissue and the associated toxicities, most commonly in the form of acute gastrointestinal symptoms related to radiation effects on the stomach, small bowel, and colon. Common modalities include 3-dimensional conformal radiation therapy (3DCRT), stereotactic body radiotherapy (SBRT), and intensity-modulated radiation therapy (IMRT). 3DCRT techniques represented one of the earliest advancements beyond crude 2-dimensional radiation delivery, and this technique was utilized in the seminal RTOG 97-04 trial of adjuvant therapy.[31] IMRT has even greater ability to limit effect on nearby tissues, notably small bowel and stomach, and can still deliver significant doses to the entire tumor volume, including the periphery.[94–96] Yovino et al. examined IMRT in 71 patients undergoing resection followed by adjuvant CRT, and found very low frequency of acute GI toxicity compared to historical toxicities in major clinical trials.[97]

The role of SBRT expanded due to ability to deliver the cumulative radiation dose in fewer fractions. SBRT is an attractive choice in the neoadjuvant setting with less interruption of systemic therapy and a shorter treatment courses. This allows for restaging and surgical resection on an earlier schedule. This same rationale applies to the adjuvant setting, where the role of long courses of radiation is called into question given the development of more effective chemotherapy regimens such as FOLFIRINOX and gemcitabine plus nab-paclitaxel. Additionally, by using higher doses in fewer fractions, SBRT may exert a greater biologic effect.[98] To date, SBRT has mainly been used for locally advanced disease, where results are encouraging.[99] Further study will elucidate its possible role for RPC and BRPC patients.

Proton therapy (PT) is a modality which offers several unique properties that can potentially increase energy delivered to the tumor tissue, with minimal effects beyond this target.[100] Indeed, PT has been studied in phase I and II trials as a neoadjuvant therapy in resectable patients.[72,101] Hong et al. found that after neoadjuvant PT and capecitabine, 77% of patients proceed to resection and median survival was 27 months for this subset undergoing surgery.[72] Local recurrence was observed in only 17% of cases. PT has been further investigated by showing minimal levels of low-grade toxicities and no high-grade toxicities.[101]

The roles of CRT and chemotherapy in locally advanced pancreatic cancer have been an active area of investigation in recent years. Initial evidence from randomized

trials suggested that chemotherapy with gemcitabine alone was superior to chemotherapy + 5-FU/cisplatin-based chemoradiation using conformal techniques.[102] A subsequent ECOG trial using similar radiation dosing with 3DCRT demonstrated a benefit of adding CRT to chemotherapy for patients with LAPC. The ECOG trial compared gemcitabine chemotherapy alone to gemcitabine-based chemoradiotherapy and systemic gemcitabine treatment. Results showed improved survival of 11.1 months for those receiving dual therapy, compared to 9.2 months for gemcitabine alone (p=0.017).[103]

The SCALOP trial was recently published which examined CRT regimens in patients with locally advanced tumors. After receiving chemotherapy with both gemcitabine and capecitabine, 74 patients were randomized to gemcitabine-based or capecitabine-based chemoradiation to a radiation dose of 50.4 Gy. Those receiving capecitabine had marginally better progression-free and overall survival, however the results were not statistically significant due to small sample sizes.[104] However, there were fewer toxicities in patients receiving capecitabine, and these results suggest a capecitabine-based regimen may be superior to gemcitabine for patients undergoing CRT.

Capecitabine-based CRT was evaluated in the LAP07 trial in which patients with LAPC underwent 4 months of chemotherapy and those without disease progression were then randomized to continue chemotherapy, or switch to CRT to 54 Gy.[105] Results showed no difference in median overall survival between the chemotherapy (16.5 months) and CRT (15.2 months) groups. Although CRT did result in a significantly decreased rate of local progression, there were no differences in proportion of patients undergoing surgery between the treatment arms (6% after chemotherapy, 3% after chemoradio-therapy). This trial calls into question the utility of 3DCRT for LAPC, and highlights the need for more effective systemic and locoregional treatments.

5. Future Directions

Historically, multi-center trials addressing neoadjuvant therapies have been challenging, with many terminating early due to poor accrual.[54–56] However, there are numerous ongoing randomized trials that seek to address many of the most pressing issues pertaining to the neoadjuvant approach. Additionally, preliminary data from a multi-institutional feasibility study show that patient accrual was better than expected, and will hopefully overcome this major barrier that hampered earlier studies.[53]

These ongoing studies will address issues such as 1) optimal timing of surgery, i.e. neoadjuvant therapy versus upfront surgery for both resectable and borderline resectable pancreatic cancer, 2) the optimal chemotherapy regimen in the neoadjuvant setting (e.g. FOLFIRINOX versus gemcitabine/nab-paclitaxel), 3) added benefit of chemoradiation versus chemotherapy alone for borderline resectable disease, 4) and potential benefit of various immunotherapy regimens and cancer vaccines. Current randomized phase II or phase III clinical trials pertaining to neoadjuvant therapy for pancreatic cancer are summarized in Table 3. The results from these multi-institutional and international studies are highly anticipated, and will shape the future direction of neoadjuvant therapy for pancreatic cancer. While surgery will remain a mainstay of treatment for patients with potentially curative disease, long-term survival will not improve until we are able to address the systemic nature of the disease through improved multi-modal care delivery.

Table 3: Ongoing Randomized Phase II/III Trials of Neoadjuvant Therapy for Pancreatic Cancer

Study ID/Title	Cancer Stage	Neoadjuvant Regimen Comparison	Study Location
NCT02839343 (Alliance Trial A021501)	BRPC	Arm1: mFOLFIRINOX Arm2: mFOLFIRINOX + XRT	USA
NCT02562716 (SWOG Trial 1505)	RPC	Arm1: mFOLFIRINOX Arm2: Gemcitabine/nab-paclitaxel	USA
NCT00727441	RPC	Arm1: GVAX Arm2: GVAX/Intravenous cyclophosphamide Arm3: GVAX/oral cyclophosphamide	USA
NCT00313560	RPC	Arm1: Erlotinib Arm2: Placebo	USA
NCT02241551	BRPC	Arm1: mFOLFIRINOX + SBRT Arm2: Gemcitabine/nab-paclitaxel + SBRT	USA
NCT01458717	BRPC	Arm1: CRT w/ gemcitabine Arm2: Upfront Surgery	Korea
NCT01521702 (NEOPAC)	RPC	Arm1: Gemcitabine/oxaliplatin Arm2: Upfront Surgery	France
NCT02919787 (NorPACT-1)	RPC	Arm1: mFOLFINIOX Arm2: Upfront surgery	Norway
NCT02676349 (PANDAS-PRODIGE 44)	BRPC	Arm1: mFOLFIRINOX + CRT Arm2: mFOLFIRINOX	France
NCT01900327 (NEOPA)	RPC	Arm1: CRT w/ gemcitabine Arm2: Upfront Surgery	Germany
NCT02717091	BRPC	Arm1: mFOLFIRINOX Arm2: Gemcitabine/nab-paclitaxel	Japan
NCT02305186 (UVA-PC-PD101)	BRPC	Arm1: CRT w/ capecitabine + pemrolizumab Arm2: CRT w/ capecitabine	USA
NCT02047513 (NEONAX)	RPC	Arm1: Upfront surgery + adjuvant gemcitabine/nab-paclitaxel Arm2: Neoadjuvant gemcitabine/nab-paclitaxel	Germany
NCT02125136 (NEOLAP)	LAPC	Arm1: mFOLFIRINOX Arm2: Gemcitabine/nab-paclitaxel	Germany
NCT02172976	RPC	Arm1: FOLFIRINOX Arm2: Upfront Surgery	Germany
NCT02439593	LAPC	Arm1: CRT Arm2: Thermo-CRT	Switzerland
NCT01150630	RPC	Arm1: Adjuvant PEXG Arm2: Neoadjuvant and adjuvant PEXG Arm3: Upfront surgery + Adjuvant gemcitabine	Italy
NCT02959879 (PANACHE01)	RPC	Arm1: FOLFOX Arm2: FOLFIRINOX Arm3: Upfront Surgery	France
NCT02446093 (PaTK02)	BRPC + LAPC	Arm1: GMCI + mFOLFIRINOX + CRT Arm2: mFOLFIRINOX + CRT	USA
NCT02336672	BRPC + LAPC	Arm1: Chemotherapy, unspecified regimen Arm2: Chemotherapy + EUS-guided cryothermal ablation	Italy

NCT01836432 (PILLAR)	BRPC + LAPC	Arm1: FOLFIRINOX + Algenpantucel-L + CRT Arm2: FOLFIRINOX + CRT Arm3: Gemcitabine/nab-paclitaxel + Algenpantucel-L + CRT Arm4: Gemcitabine/nab-paclitaxel + CRT	USA

RPC: Resectable Pancreatic Cancer. BRPC: Borderline Resectable Pancreatic Cancer. LAPC: Locally advanced, unresectable pancreatic cancer. 5-FU: XRT: External Beam Radiation Therapy. SBRT: Stereotactic body radiation therapy. CRT: Chemoradiotherapy. FOLFIRINOX: Folinic acid, 5-FU, irinotecan, oxaliplatin. mFOLFIRINOX: modified FOLFIRINOX. PEXG: cisplatin, epirubicin, gemcitabine, capecitabine. GMCI: gene-mediated cytotoxic immunotherapy. EUS: endoscopic ultrasound.

6. References

1. American Cancer Society. *Cancer Facts and Figures 2016*. Atlanta; 2016. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2016/cancer-facts-and-figures-2016.pdf. Accessed June 13, 2017.

2. Matrisian LM, Aizenberg R, Rosenzweig A. The alarming rise of pancreatic cancer deaths in the United states: Why we need to stem the tide today. *Pancreat Cancer Action Network; Exec Summ*. 2012.

3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703. doi:10.1056/NEJMoa1304369.

4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *N Engl J Med*. 2011;364(19):1817-1825. doi:10.1056/NEJMoa1011923.

5. National Comprehensive Cancer Network. NCCN Guidelines Version 2.2017 Pancreatic Adenocarcinmoa. *NCCN.org*. 2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed June 13, 2017.

6. Katz MHG, Wang H, Fleming JB, et al. Long-Term Survival After Multidisciplinary Management of Resected Pancreatic Adenocarcinoma. *Ann Surg Oncol*. 2009;16(4):836-847. doi:10.1245/s10434-008-0295-2.

7. Dimou F, Sineshaw H, Parmar AD, Tamirisa NP, Jemal A, Riall TS. Trends in Receipt and Timing of Multimodality Therapy in Early-Stage Pancreatic Cancer. *J Gastrointest Surg*. 2016;20(1):93-103; discussion 103. doi:10.1007/s11605-015-2952-7.

8. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg*. 2007;246(1):52-60. doi:10.1097/01.sla.0000259391.84304.2b.

9. WINTER J, CAMERON J, CAMPBELL K, et al. 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience? *J Gastrointest Surg*. 2006;10(9):1199-1211. doi:10.1016/j.gassur.2006.08.018.

10. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008;26(21):3496-3502. doi:10.1200/JCO.2007.15.8634.

11. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol*. 2008;26(21):3487-3495. doi:10.1200/JCO.2007.15.8642.

12. Abbott DE, Tzeng C-WD, Merkow RP, et al. The Cost-Effectiveness of Neoadjuvant Chemoradiation is Superior to a Surgery-First Approach in the Treatment of Pancreatic Head Adenocarcinoma. *Ann Surg Oncol*. 2013;20(S3):500-508.

doi:10.1245/s10434-013-2882-0.

13. Chang DK, Johns AL, Merrett ND, et al. Margin Clearance and Outcome in Resected Pancreatic Cancer. *J Clin Oncol*. 2009;27(17):2855-2862. doi:10.1200/JCO.2008.20.5104.

14. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg*. 2001;234(6):758-768. http://www.ncbi.nlm.nih.gov/pubmed/11729382. Accessed June 13, 2017.

15. Petrelli F, Coinu A, Borgonovo K, et al. FOLFIRINOX-Based Neoadjuvant Therapy in Borderline Resectable or Unresectable Pancreatic Cancer. *Pancreas*. 2015;44(4):515-521. doi:10.1097/MPA.0000000000000314.

16. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. *J Gastrointest Surg*. 5(2):121-130. http://www.ncbi.nlm.nih.gov/pubmed/11331473. Accessed July 7, 2017.

17. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. *J Clin Oncol*. 1997;15(3):928-937. doi:10.1200/JCO.1997.15.3.928.

18. Aloia TE, Lee JE, Vauthey J-N, et al. Delayed Recovery after Pancreaticoduodenectomy: A Major Factor Impairing the Delivery of Adjuvant Therapy? *J Am Coll Surg*. 2007;204(3):347-355. doi:10.1016/j.jamcollsurg.2006.12.011.

19. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol*. 2001;8(10):758-765. http://www.ncbi.nlm.nih.gov/pubmed/11776488. Accessed June 30, 2017.

20. Palmer DH, Stocken DD, Hewitt H, et al. A Randomized Phase 2 Trial of Neoadjuvant Chemotherapy in Resectable Pancreatic Cancer: Gemcitabine Alone Versus Gemcitabine Combined with Cisplatin. *Ann Surg Oncol*. 2007;14(7):2088-2096. doi:10.1245/s10434-007-9384-x.

21. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. Seiler C, ed. *PLoS Med*. 2010;7(4):e1000267. doi:10.1371/journal.pmed.1000267.

22. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg*. 2004;91(5):586-594. doi:10.1002/bjs.4484.

23. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin*. 55(1):10-30. http://www.ncbi.nlm.nih.gov/pubmed/15661684. Accessed June 22, 2017.

24. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation

and chemotherapy following curative resection. *Arch Surg*. 1985;120(8):899-903. http://www.ncbi.nlm.nih.gov/pubmed/4015380. Accessed June 29, 2017.

25. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. *Cancer*. 1987;59(12):2006-2010. http://www.ncbi.nlm.nih.gov/pubmed/3567862. Accessed June 29, 2017.

26. Bakkevold KE, Arnesjø B, Dahl O, Kambestad B. Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater--results of a controlled, prospective, randomised multicentre study. *Eur J Cancer*. 1993;29A(5):698-703. http://www.ncbi.nlm.nih.gov/pubmed/8471327. Accessed July 21, 2017.

27. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. *Ann Surg*. 1999;230(6):776-82-4. http://www.ncbi.nlm.nih.gov/pubmed/10615932. Accessed July 21, 2017.

28. Neoptolemos JP, Stocken DD, Friess H, et al. A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer. *N Engl J Med*. 2004;350(12):1200-1210. doi:10.1056/NEJMoa032295.

29. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007;297(3):267-277. doi:10.1001/jama.297.3.267.

30. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer. *JAMA*. 2013;310(14):1473. doi:10.1001/jama.2013.279201.

31. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA*. 2008;299(9):1019-1026. doi:10.1001/jama.299.9.1019.

32. Van Laethem J-L, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol*. 2010;28(29):4450-4456. doi:10.1200/JCO.2010.30.3446.

33. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. *J Clin Oncol*. 2012;30(33):4077-4083. doi:10.1200/JCO.2011.38.2960.

34. Pilepich M V, Miller HH. Preoperative irradiation in carcinoma of the pancreas. *Cancer*. 1980;46(9):1945-

1949. http://www.ncbi.nlm.nih.gov/pubmed/7427900. Accessed June 22, 2017.

35. Jessup JM, Steele G, Mayer RJ, et al. Neoadjuvant therapy for unresectable pancreatic adenocarcinoma. *Arch Surg*. 1993;128(5):559-564. http://www.ncbi.nlm.nih.gov/pubmed/8098206. Accessed June 22, 2017.

36. Hoffman JP, Weese JL, Solin LJ, et al. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. *Am J Surg*. 1995;169(1):71-7-8. http://www.ncbi.nlm.nih.gov/pubmed/7818001. Accessed June 22, 2017.

37. Fogelman DR, Chen J, Chabot JA, et al. The evolution of adjuvant and neoadjuvant chemotherapy and radiation for advanced pancreatic cancer: from 5-fluorouracil to GTX. *Surg Oncol Clin N Am*. 2004;13(4):711-35, x. doi:10.1016/j.soc.2004.06.005.

38. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst*. 1988;80(10):751-755. http://www.ncbi.nlm.nih.gov/pubmed/2898536. Accessed June 22, 2017.

39. Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Gastrointestinal Tumor Study Group. *Cancer*. 1985;56(11):2563-2568. http://www.ncbi.nlm.nih.gov/pubmed/2864997. Accessed June 22, 2017.

40. Pisters PWT, Wolff RA, Crane CH, Evans DB. Combined-modality treatment for operable pancreatic adenocarcinoma. *Oncology (Williston Park)*. 2005;19(3):393-404, 409-10, 412-416. http://www.ncbi.nlm.nih.gov/pubmed/15828554. Accessed June 29, 2017.

41. Evans DB, Multidisciplinary Pancreatic Cancer Study Group for the MPCS. Resectable pancreatic cancer: the role for neoadjuvant/preoperative therapy. *HPB (Oxford)*. 2006;8(5):365-368. doi:10.1080/13651820600804005.

42. White RR, Tyler DS. Neoadjuvant therapy for pancreatic cancer: the Duke experience. *Surg Oncol Clin N Am*. 2004;13(4):675-684. doi:10.1016/j.soc.2004.06.001.

43. Smeenk HG, de Castro SMM, Jeekel JJ, et al. Locally Advanced Pancreatic Cancer Treated with Radiation and 5-Fluorouracil: A First Step to Neoadjuvant Treatment? *Dig Surg*. 2005;22(3):191-197. doi:10.1159/000087973.

44. Abrams RA, Lillemoe KD, Piantadosi S. Continuing controversy over adjuvant therapy of pancreatic cancer. *Lancet (London, England)*. 2001;358(9293):1565-1566. doi:10.1016/S0140-6736(01)06666-1.

45. Choti MA. Adjuvant Therapy for Pancreatic Cancer — The Debate Continues. *N Engl J Med*. 2004;350(12):1249-1251. doi:10.1056/NEJMe048002.

46. Morris SL, Beasley M, Leslie M. Chemotherapy for Pancreatic Cancer. *N Engl J Med*. 2004;350(26):2713-2715.

doi:10.1056/NEJM200406243502617.

47. Bydder S, Spry N. Chemotherapy for pancreatic cancer. *N Engl J Med*. 2004;350(26):2713-5-5. http://www.ncbi.nlm.nih.gov/pubmed/15218576. Accessed June 30, 2017.

48. Crane CH, Ben-Josef E, Small W. Chemotherapy for pancreatic cancer. *N Engl J Med*. 2004;350(26):2713-5-5. http://www.ncbi.nlm.nih.gov/pubmed/15218575. Accessed June 30, 2017.

49. Merchant NB, Rymer J, Koehler EAS, et al. Adjuvant Chemoradiation Therapy for Pancreatic Adenocarcinoma: Who Really Benefits? *J Am Coll Surg*. 2009;208(5):829-838. doi:10.1016/j.jamcollsurg.2008.12.020.

50. Parikh AA, Maiga A, Bentrem D, et al. Adjuvant Therapy in Pancreas Cancer: Does It Influence Patterns of Recurrence? *J Am Coll Surg*. 2016;222(4):448-456. doi:10.1016/j.jamcollsurg.2015.12.031.

51. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403-2413. doi:10.1200/JCO.1997.15.6.2403.

52. Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol*. 2012;19(5):1644-1662. doi:10.1245/s10434-011-2110-8.

53. Katz MHG, Shi Q, Ahmad SA, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg*. 2016;151(8):e161137. doi:10.1001/jamasurg.2016.1137.

54. Landry J, Catalano PJ, Staley C, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. *J Surg Oncol*. 2010;101(7):587-592. doi:10.1002/jso.21527.

55. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer. *Strahlentherapie und Onkol*. 2015;191(1):7-16. doi:10.1007/s00066-014-0737-7.

56. Casadei R, Di Marco M, Ricci C, et al. Neoadjuvant Chemoradiotherapy and Surgery Versus Surgery Alone in Resectable Pancreatic Cancer: A Single-Center Prospective, Randomized, Controlled Trial Which Failed to Achieve Accrual Targets. *J Gastrointest Surg*. 2015;19(10):1802-1812. doi:10.1007/s11605-015-2890-4.

57. Talamonti MS, Small W, Mulcahy MF, et al. A Multi-Institutional Phase II Trial of Preoperative Full-Dose Gemcitabine and Concurrent Radiation for Patients With Potentially Resectable Pancreatic Carcinoma. *Ann Surg Oncol*. 2006;13(2):150-158.

doi:10.1245/ASO.2006.03.039.

58. Mornex F, Girard N, Scoazec J-Y, et al. Feasibility of preoperative combined radiation therapy and chemotherapy with 5-fluorouracil and cisplatin in potentially resectable pancreatic adenocarcinoma: The French SFRO-FFCD 97-04 Phase II trial. *Int J Radiat Oncol*. 2006;65(5):1471-1478. doi:10.1016/j.ijrobp.2006.02.054.

59. Heinrich S, Pestalozzi BC, Schäfer M, et al. Prospective Phase II Trial of Neoadjuvant Chemotherapy With Gemcitabine and Cisplatin for Resectable Adenocarcinoma of the Pancreatic Head. *J Clin Oncol*. 2008;26(15):2526-2531. doi:10.1200/JCO.2007.15.5556.

60. Turrini O, Ychou M, Moureau-Zabotto L, et al. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: New neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol*. 2010;36(10):987-992. doi:10.1016/j.ejso.2010.07.003.

61. Sahora K, Kuehrer I, Eisenhut A, et al. NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer. *Surgery*. 2011;149(3):311-320. doi:10.1016/j.surg.2010.07.048.

62. Sahora K, Kuehrer I, Schindl M, Koelblinger C, Goetzinger P, Gnant M. NeoGemTax: Gemcitabine and Docetaxel as Neoadjuvant Treatment for Locally Advanced Nonmetastasized Pancreatic Cancer. *World J Surg*. 2011;35(7):1580-1589. doi:10.1007/s00268-011-1113-8.

63. Lee J-L, Kim SC, Kim J-H, et al. Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma. *Surgery*. 2012;152(5):851-862. doi:10.1016/j.surg.2012.03.010.

64. Pipas JM, Zaki BI, McGowan MM, et al. Neoadjuvant cetuximab, twice-weekly gemcitabine, and intensity-modulated radiotherapy (IMRT) in patients with pancreatic adenocarcinoma. *Ann Oncol Off J Eur Soc Med Oncol*. 2012;23(11):2820-2827. doi:10.1093/annonc/mds109.

65. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer*. 2013;119(15):2692-2700. doi:10.1002/cncr.28117.

66. Shinoto M, Yamada S, Yasuda S, et al. Phase 1 trial of preoperative, short-course carbon-ion radiotherapy for patients with resectable pancreatic cancer. *Cancer*. 2013;119(1):45-51. doi:10.1002/cncr.27723.

67. Tinchon C, Hubmann E, Pichler A, et al. Safety and efficacy of neoadjuvant FOLFIRINOX treatment in a series of patients with borderline resectable pancreatic ductal adenocarcinoma. *Acta Oncol (Madr)*. 2013;52(6):1231-1233. doi:10.3109/0284186X.2013.771821.

68. Motoi F, Ishida K, Fujishima F, et al. Neoadjuvant Chemotherapy with Gemcitabine and S-1 for Resectable and Borderline Pancreatic Ductal Adenocarcinoma: Results from a

Prospective Multi-institutional Phase 2 Trial. *Ann Surg Oncol*. 2013;20(12):3794-3801. doi:10.1245/s10434-013-3129-9.

69. Wo JY, Mamon HJ, Ferrone CR, et al. Phase I study of neoadjuvant accelerated short course radiation therapy with photons and capecitabine for resectable pancreatic cancer. *Radiother Oncol*. 2014;110(1):160-164. doi:10.1016/j.radonc.2013.10.027.

70. Sahora K, Schindl M, Kuehrer I, et al. A phase II trial of two durations of Bevacizumab added to neoadjuvant gemcitabine for borderline and locally advanced pancreatic cancer. *Anticancer Res*. 2014;34(5):2377-2384. http://www.ncbi.nlm.nih.gov/pubmed/24778046. Accessed July 18, 2017.

71. O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A Single-Arm, Nonrandomized Phase II Trial of Neoadjuvant Gemcitabine and Oxaliplatin in Patients With Resectable Pancreas Adenocarcinoma. *Ann Surg*. 2014;260(1):142-148. doi:10.1097/SLA.0000000000000251.

72. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2014;89(4):830-838. doi:10.1016/j.ijrobp.2014.03.034.

73. Chan E, Arlinghaus LR, Cardin DB, et al. Phase I trial of vorinostat added to chemoradiation with capecitabine in pancreatic cancer. *Radiother Oncol*. 2016;119(2):312-318. doi:10.1016/j.radonc.2016.04.013.

74. Masui T, Doi R, Kawaguchi Y, et al. Concurrent gemcitabine+S-1 neoadjuvant chemotherapy contributes to the improved survival of patients with small borderline-resectable pancreatic cancer tumors. *Surg Today*. 2016;46(11):1282-1289. doi:10.1007/s00595-016-1310-z.

75. OKADA K-I, HIRONO S, KAWAI M, et al. Phase I Study of Nab–Paclitaxel plus Gemcitabine as Neoadjuvant Therapy for Borderline Resectable Pancreatic Cancer. *Anticancer Res*. 2017;37(2):853-858. doi:10.21873/anticanres.11389.

76. Nagakawa Y, Hosokawa Y, Nakayama H, et al. A phase II trial of neoadjuvant chemoradiotherapy with intensity-modulated radiotherapy combined with gemcitabine and S-1 for borderline-resectable pancreatic cancer with arterial involvement. *Cancer Chemother Pharmacol*. 2017;79(5):951-957. doi:10.1007/s00280-017-3288-7.

77. Joensuu TK, Kiviluoto T, Kärkkäinen P, et al. Phase I-II trial of twice-weekly gemcitabine and concomitant irradiation in patients undergoing pancreaticoduodenectomy with extended lymphadenectomy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2004;60(2):444-452. doi:10.1016/j.ijrobp.2004.03.026.

78. Ohigashi H, Ishikawa O, Eguchi H, et al. Feasibility and Efficacy of Combination Therapy With Preoperative Full-Dose Gemcitabine, Concurrent Three-Dimensional Conformal Radiation, Surgery, and Postoperative Liver Perfusion

Chemotherapy for T3-Pancreatic Cancer. *Ann Surg*. 2009;250(1):88-95. doi:10.1097/SLA.0b013e3181ad65cc.

79. Small W, Mulcahy MF, Rademaker A, et al. Phase II Trial of Full-Dose Gemcitabine and Bevacizumab in Combination With Attenuated Three-Dimensional Conformal Radiotherapy in Patients With Localized Pancreatic Cancer. *Int J Radiat Oncol*. 2011;80(2):476-482. doi:10.1016/j.ijrobp.2010.02.030.

80. Laurent S, Monsaert E, Boterberg T, et al. Feasibility of radiotherapy with concomitant gemcitabine and oxaliplatin in locally advanced pancreatic cancer and distal cholangiocarcinoma: a prospective dose finding phase I-II study. *Ann Oncol Off J Eur Soc Med Oncol*. 2009;20(8):1369-1374. doi:10.1093/annonc/mdp005.

81. Pipas JM, Barth RJ, Zaki B, et al. Docetaxel/Gemcitabine Followed by Gemcitabine and External Beam Radiotherapy in Patients With Pancreatic Adenocarcinoma. *Ann Surg Oncol*. 2005;12(12):995-1004. doi:10.1245/ASO.2005.04.503.

82. Alvarez R, Musteanu M, Garcia-Garcia E, et al. Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. *Br J Cancer*. 2013;109(4):926-933. doi:10.1038/bjc.2013.415.

83. Ielpo B, Duran H, Diaz E, et al. Preoperative treatment with gemcitabine plus nab-paclitaxel is a safe and effective chemotherapy for pancreatic adenocarcinoma. *Eur J Surg Oncol*. 2016;42(9):1394-1400. doi:10.1016/j.ejso.2016.01.006.

84. Blazer M, Wu C, Goldberg RM, et al. Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas. *Ann Surg Oncol*. 2015;22(4):1153-1159. doi:10.1245/s10434-014-4225-1.

85. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer. *Ann Surg*. 2016;264(3):457-463. doi:10.1097/SLA.0000000000001850.

86. Kim SS, Nakakura EK, Wang ZJ, et al. Preoperative FOLFIRINOX for borderline resectable pancreatic cancer: Is radiation necessary in the modern era of chemotherapy? *J Surg Oncol*. 2016;114(5):587-596. doi:10.1002/jso.24375.

87. Roldan GE, Gunderson LL, Nagorney DM, et al. External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. *Cancer*. 1988;61(6):1110-1116. http://www.ncbi.nlm.nih.gov/pubmed/3342371. Accessed July 6, 2017.

88. Herskovic A, Martz K, Al-Sarraf M, et al. Combined Chemotherapy and Radiotherapy Compared with Radiotherapy Alone in Patients with Cancer of the Esophagus. *N Engl J Med*. 1992;326(24):1593-1598. doi:10.1056/NEJM199206113262403.

89. Wong RK, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. In: Wong RK, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006:CD002092.

doi:10.1002/14651858.CD002092.pub2.

90. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA*. 1999;281(17):1623-1627. http://www.ncbi.nlm.nih.gov/pubmed/10235156. Accessed July 6, 2017.

91. Bernier J, Domenge C, Ozsahin M, et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. *N Engl J Med*. 2004;350(19):1945-1952. doi:10.1056/NEJMoa032641.

92. Ragaz J, Jackson SM, Le N, et al. Adjuvant Radiotherapy and Chemotherapy in Node-Positive Premenopausal Women with Breast Cancer. *N Engl J Med*. 1997;337(14):956-962. doi:10.1056/NEJM199710023371402.

93. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. *DPC4* Gene Status of the Primary Carcinoma Correlates With Patterns of Failure in Patients With Pancreatic Cancer. *J Clin Oncol*. 2009;27(11):1806-1813. doi:10.1200/JCO.2008.17.7188.

94. van der Geld YG, van Triest B, Verbakel WFAR, et al. Evaluation of Four-Dimensional Computed Tomography-Based Intensity-Modulated and Respiratory-Gated Radiotherapy Techniques for Pancreatic Carcinoma. *Int J Radiat Oncol*. 2008;72(4):1215-1220. doi:10.1016/j.ijrobp.2008.07.010.

95. Kataria T, Rawat S, Sinha SN, et al. Intensity modulated radiotherapy in abdominal malignancies: our experience in reducing the dose to normal structures as compared to the gross tumor. *J Cancer Res Ther*. 2(4):161-165. http://www.ncbi.nlm.nih.gov/pubmed/17998698. Accessed July 5, 2017.

96. Brown MW, Ning H, Arora B, et al. A dosimetric analysis of dose escalation using two intensity-modulated radiation therapy techniques in locally advanced pancreatic carcinoma. *Int J Radiat Oncol Biol Phys*. 2006;65(1):274-283. doi:10.1016/j.ijrobp.2006.01.003.

97. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys*. 2011;79(1):158-162. doi:10.1016/j.ijrobp.2009.10.043.

98. Marcu LG. Altered fractionation in radiotherapy: From radiobiological rationale to therapeutic gain. *Cancer Treat Rev*. 2010;36(8):606-614. doi:10.1016/j.ctrv.2010.04.004.

99. Chhabra A, Kaiser A, Regine WF, Chuong MD. The expanding role of stereotactic body radiation therapy for pancreatic cancer: a review of the literature. *Transl Cancer Res*. 2015;4(6):659-670. doi:10.21037/5996.

100. Nichols RC, Huh S, Li Z, Rutenberg M. Proton therapy for pancreatic cancer. *World J Gastrointest Oncol*. 2015;7(9):141. doi:10.4251/wjgo.v7.i9.141.

101. Nichols RC, George TJ, Zaiden RA, et al. Proton therapy with concomitant

capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncol*. 2013;52(3):498-505. doi:10.3109/0284186X.2012.762997.

102. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol*. 2008;19(9):1592-1599. doi:10.1093/annonc/mdn281.

103. Loehrer PJ, Feng Y, Cardenes H, et al. Gemcitabine Alone Versus Gemcitabine Plus Radiotherapy in Patients With Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial. *J Clin Oncol*. 2011;29(31):4105-4112. doi:10.1200/JCO.2011.34.8904.

104. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol*. 2013;14(4):317-326. doi:10.1016/S1470-2045(13)70021-4.

105. Hammel P, Huguet F, van Laethem J-L, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib. *JAMA*. 2016;315(17):1844. doi:10.1001/jama.2016.4324.

