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| **Table 1.** Operational definitions of resectability of pancreatic cancer | | |
| **Classification of Resectability of Pancreatic Cancer** | **Definition by AHPBA/SSO/SSAT** | **Definition by MD Anderson Cancer Centre** |
| **Resectable** | The tumor does not abut or encase any of the following vascular structures: the superior mesenteric vein or portal vein, superior mesenteric artery or common hepatic artery or celiac trunk. | The tumor abuts or encases the superior mesenteric vein or portal vein without occluding the lumen. Absence of abutment or encasement of the superior mesenteric artery, common hepatic artery or celiac trunk. |
| **Borderline Resectable** | Abutment, encasement or occlusion of the superior mesenteric vein or portal vein. Abutment of the superior mesenteric artery. Abutment or short segment encasement of the common hepatic artery. Absence or abutment or encasement of the celiac trunk. | Tumor causing a short-segment occlusion of the superior mesenteric vein or portal vein. Presence of abutment of the superior mesenteric artery, abutment or encasement of a short segment of the common hepatic artery, absence of abutment or encasement of the celiac trunk. |
| **Locally Advanced** | Tumor located in the proximity of the superior mesenteric vein or portal vein and the superior mesenteric vein or portal vein are unable to be resected and reconstructed. Tumor encasing the superior mesenteric artery, or long-segment encasement of the common hepatic artery, or abutment of the celiac trunk. | Tumor located in the proximity of the superior mesenteric vein or portal vein that are not reconstructible. Presence of tumor encasement of the superior mesenteric artery, long-segment encasement of the common hepatic artery and encasement of the celiac trunk. |

**Abbreviations:** (AHPBA) Americas Hepato-Pancreato-Biliary Association; (SSO) Society of Surgical Oncology; (SSAT) Society for Surgery of the Alimentary Tract

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| **Table 2:** Summary of the benefits and drawbacks of neo-adjuvant and adjuvant therapies for the treatment of patients with resectable pancreatic cancer | | | |
| **Neo-adjuvant Therapy** | | **Adjuvant Therapy** | |
| **Advantages** | **Disadvantages** | **Advantages** | **Disadvantages** |
| In comparison to the strategy of adjuvant chemotherapy or chemoradiation therapy where up to 50% of patients who undergo surgery cannot complete their therapy due to complications or decline of their function, neoadjuvant strategy has been shown to be well tolerated by the majority of patients and therefore a greater proportion receive systemic therapy | Neoadjuvant therapy requires the placement of biliary stents to decompress the biliary obstruction prior to surgery of patients with jaundice. The placement of biliary stents before surgery increases the risk of infections in the perioperative period. | One of the advantages of surgery first approach is that patients have a short period of time between when they are diagnosed and when they undergo resections of their tumor. This might have some benefits on patients' and their families’ anxiety. | About 20-50% of patients will not be able to complete their postoperative therapy due to surgical complications or overall decline of their performance status. |
| The use of neo-adjuvant therapy might sterilize the presence of small metastatic disease and reduce the size of the primary tumor. Downsizing the primary tumor might increase the likelihood of negative resection margins. | Pre-operative therapy delays surgery and increases the risk of progression of the disease to the point of becoming unresectable | Since patients undergo surgery as soon as possible after their diagnosis, their risk of tumor progression is smaller than patients who wait a longer time before being operated on. | One of the risk of undergoing surgery first for pancreatic cancer is that, some patients will undergo a major operation without the benefit of being cured as they might already have micrometastases.. |
| Treating patients before surgery, gives physicians some time to identify the tumors with poor prognosis that do not respond to the therapy. The identification of those patients who are likely to experience early metastases is very important because prevents them to undergo unnecessary surgery. | The use of neoadjuvant therapies might increase the risk of perioperative morbidity and mortality due to the side effects of chemotherapy or chemoradiation. | Patients who undergo surgery first do not routinely need the placement of biliary stents to release their jaundice before undergoing resection. | Patients who undergo surgery first have a higher risk of positive resection margins. |
| One of the advantages of using chemotherapy or chemoradiation therapy before surgery is that the blood supply to the pancreatic tumor is not compromised by the ligation of vessels. Therefore, chemotherapy agents can be delivered to the pancreatic tumor in higher concentrations. |  |  |  |

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| **Table 3:** Phase I and Phase II studies assessing the outcomes of patients with resectable pancreatic cancer treated with neoadjuvant therapies | | | | | | | | |
| **Author (Year) / Journal /Trial / Institution** | **N. Patients** | **Clinical Stage / Duration of Neoadjuvant**  **Therapy** | **Study Design** | **Chemotherapy / Chemoradiation** | **Radiological Response** | **Resection Rate (%)** | **Negative Resection Margins (%)** | **Median Overall Survival (Months)** |
| Hoffman [28](1998)/ J Clin Oncol / ECOG | 53 | Resectable PC / 2.8 months | Phase II, prospective study, November 1991 to September 1993 | 5-FU (1000 mg/m2)per day + Mitomycin C (10 mg/m2)+RT (50 Gy) | Partial response 8%; Stable disease78%; Progression 16% | 45 | 67 | 15 with surgery; without surgery 8; 10.9 for the entire cohort |
| PistersPister[29] (2002)/ J Clin Oncol / MD Anderson Cancer Centre | 35 | Resectable PC / 1.8 months | Phase II, prospective study, timeframe not specified. | Paclitaxel (60 mg/m2) weekly, RT (30Gy) | Partial response 4%; Stable disease 23%; Progression 20% | 57 | 68 | 12 for the entire cohort; 19 with surgery; 10 without surgery |
| Joensuu [30](2004)/ Int J Radiat Oncol Biol Phys / Helsinki University | 28 | Resectable PC / 3.5 months | Phase I-II prospective study, November 1999 to December 2001 | Gemcitabine (20 mg/m2 vs 50 mg/m2 vs 100 mg/m2) twice a week + RT (50 GY) | n.a. | 71 | n.a. | 13.6 for the entire cohort; |
| Talamonti[31] (2006)/ Ann Surg Oncol/ Northwestern University | 20 | Resectable PC /3.8 months | Phase II prospective, multi-institutional study, April 2002 to October 2003 | Gemcitabine (1000 mg/m2 weekly) + RT (36 Gy) | Partial response 15%; Stable disease 80%; Progression 5% | 85 | 94 | 26 months with surgery; |
| Palmer [32](2007)/ Ann Surg Oncol/ University of Birmingham | 24 | Resectable PC / 4 months | Phase II, prospective study, November 1999 to May 2003 | Gemcitabine (1000 mg/m2 weekly) | Partial Response 0%; Stable Disease 29%; Progression 4%; Unable to measure 4% | 38 | 75 | 28.4 with surgery; 9.9 for the entire cohort |
| Palmer [32](2007)/ Ann Surg Oncol/ University of Birmingham | 26 | Resectable PC / 4 months | Phase II, prospective study, November 1999 to May 2003 | Gemcitabine (1000 mg/m2 weekly) + Cisplatin (25 mg/m2) | Partial Response 0%; Stable Disease 66%; Progression 21%; Unable to measure 4% | 70 | 75 | 28.4 with surgery; 9.9 for the entire cohort |
| Le Scodan[33] (2009)/ Ann Oncol/ SFRO-FFCD | 41 | Resectable PC / 3 months | Phase II, prospective study, January 1998 to March 2003 | RT (50 Gy) + 5-FU (300 mg/m2 daily) + Cisplatin (20 mg/m2) | Partial response 10%; Stable Disease 65%; Progression 25% | 63 | 81 | 11.7 with surgery; 9.4 for the entire cohort |
| Heinrich [34](2008)/ Ann Surg/ University Hospital of Zurich | 28 | Resectable PC / 2 months | Phase II, prospective study, August 2001 to April 2007 | Gemcitabine (1000 mg/m2 twice weekly) + Cisplatin (50 mg/m2) | Partial response 4%; Stable Disease 61%; Progression 13%; | 89 | 80 | 19.1 months with surgery |
| Evans[35] (2008)/ J Clin Oncol/ MD Anderson Cancer Centre | 80 | Resectable PC / 3 months | Phase II, prospective study, July 1998 to October 2001 | Gemcitabine (400 mg/m2 weekly) + RT (30 Gy) | n.a. | 85 | 82 | 34 months with surgery; 22.7 months for the entire cohort; 7 months without surgery |
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| Varadhachari[36] (2008) / J Clin Oncol/ MD Anderson Cancer Centre | 90 | Resectable PC / 4.3 months | Phase II, prospective study, October 2002 to February 2006 | Gemcitabine (750 mg/m2 weekly) + Cisplatin (30 mg/m2) every 2 weeks + RT (30 Gy) | n.a. | 58 | 96 | 31.0 months with surgery; 17.4 months for the entire cohort; 10.5 months without surgery |
| Turrini[37] (2009) / Oncology /University Mediterranean | 34 | Resectable PC / 2.1 months | Phase II, prospective study, May 2003 to July 2005 | Docetazel (30mg/m2) weekly + RT (45 GY) | Partial response 9%; Stable disease 59%; Progression 32% | 68 | 100 | 32 months with surgery; 15.5 months for entire cohort; 11 months without surgery |
| Landry[38] (2010)/ J Surg Oncol/ Emory University/ Multicenter ECOG | 21 | Resectable PC / 3 months | Phase II, prospective two-arm study, October 2013 to June 2015 | **Arm A:** Gemcitabine (500 mg/m2) weekly + RT (50Gy) **Arm B:** Gemcitabine (175 mg/m2) + Cisplatin (20 mg/m2) + 5-FU (600 mg/m2) + RT (50Gy) | Arm A: Partial response 10%, Arm B: Partial response 18.2% | n.a. | n.a. | Arm A: entire cohort 19.4 months. Arm B: entire cohort 13.4 months. 26.3 months with surgery |
| Wo[39] (2014)/Radiother Oncol / Multicentric | 10 | Resectable PC | Phase I, prospective study | Capecitabine (1650 mg/m2) over 10 days + RT (30 Gy) | n.a. | 80 | n.a. | n.a. |
| Shinoto[40] (2013)/ Cancer / Japan | 26 | Resetable PC | Phase I, prospective study, April 2003 to December 2010 | RT (30Gy) | Partial response 3.8%; Stable disease 96.1% | 81 | 90 | 18.6 months for entire cohort; n.a. for patients who underwent surgery |
| O'Reilly [41](2014)/ Ann Surg/ Memorial Sloan Kettering Cancer Centre | 38 | Resectable PC | Phase II, prospective study, July 2007 to December 2011 | Gemcitabine (1000 mg/m2) + Oxaliplatin (80 mg/m2) every 2 weeks | Partial response 10.5%; Stable disease 73.7%; Progression 7.9%; n.a. 7.9% | 77 | 74 | 27.2 months for the enire cohort; 22 months progrsession free survival with surgery; |
| Golcher[42] (2015)/ Strahlenther Onkol/ Germany | 66 (33 patients allocated to surgery + 33 patients allocated to chemoradiation followed by surgery) | Resectable PC | Phase II, prospective randomized trial with two arms: primary surgery vs. preoperative chemoradiation followed by surgery. June 2003 to December 2009 | Gemcitabine (300 mg/m2) + Cisplatin (30 mg /m2) + RT (50.4 Gy) [Preoperative for patients enrolled in Arm A] | n.a. | Preoperative chemoradiation: 69% Surgery first: 57% | Arm A (preoperative chemoradition): 48. Arm B (surgery first): 51 | Arm A (preoperative chemoradiation): 18.9 months. Arm B (surgery first): 25.0 months. |
| Van Buren[43] (2013)/ Ann Surg Oncol/ Multicenter/ USA | 59 | Resectable PC | Phase II, prospective study, February 2007 to February 2011 | Gemcitabine (1500 mg/m2) ever 2 weeks + Bevacizumab (10 mg/kg) + RT (30 Gy) | Partial response 8.4%; Stable disease 73.7%; Progression 7.9% | 74 | 88 | 19.7 months with surgery; 16.8 months for the entire cohort; |

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| **Table 4.** List of ongoing phase II and phase III trials comparing neoadjuvant therapies versus adjuvant strategies for resectable pancreatic adenocarcinoma. | | | | |
| **Study** | **Design** | **Number of Patients Needed** | **Therapy** | **Primary Outcome** |
| **NEOPAC (NCT01314027)** | Phase III Enrollment 2009-2014 | 350 | Neoadjuvant gemcitabine/oxaliplatin + adjuvant gemcitabine vs. Adjuvant gemcitabine | Progression free survival |
| **NEOPAC (NCT01521702)** | Phase III Initiated in 2011 | 310 | Preoperative FOLFIRINOX, followed by adjuvant gemcitabine after surgery vs. adjuvant gemcitabine after resection | Five-year progression free survival |
| [**NCT01900327**](ctgov:NCT01900327) | Phase III | 410 | Neoadjuvant gemcitabine-based chemoradiation therapy followed by adjuvant gemcitabine vs. adjuvant gemcitabine | Three-year overall survival |
| [**NCT01771146**](ctgov:NCT01771146) | Phase II | 100 | Neoadjuvant FOLFIRINOX | Progression free survival |
| **NEONAX (NCT02047513)** | Randomized phase II | 166 | Neoadjuvant gemcitabine + nab-paclitaxel followed by adjuvant gemcitabine + nab-paclitaxel vs. adjuvant gemcitabine + nab-paclitaxel | Disease-free survival at 18 months |
| [**NCT01150630**](ctgov:NCT01150630) | Randomized phase II/III | 370 | Adjuvant PEXG vs. adjuvant gemcitabine vs. neoadjuvant PEXG -followed by surgery and then adjuvant PEXG | One year event-free survival |
| **ACOSOG-Z5041**  **(NCT00733746)** | Phase II | 123 | Neoadjuvant gemcitabine + erlotinib (completed; results pending) | Two-year overall survival |
| [**NCT00727441**](ctgov:NCT00727441) | Phase II | 87 | Neoadjuvant GVAX +/- IV or oral cyclophosphamide followed by adjuvant gemcitabine + CRT | Safety, feasibility, and immune response |
| [**NCT02178709**](ctgov:NCT02178709) | Phase II | 48 | Neoadjuvant FOLFIRINOX | Pathologic complete response |
| **GEMCAD1003 (NCT01389440)** | Phase II | 24 | Neoadjuvant gemcitabine + erlotinib | R0 resection rate |
| **NCT02562716** | Phase II Enrollment 2015-2019 | 112 | Neoadjuvant and adjuvant mFOLFIRINOX vs. neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine | Overall survival |
| [**NCT02243007**](ctgov:NCT02243007) | Randomized phase II | 112 | Neoadjuvant FOLFIRINOX vs gemcitabine + nab-paclitaxel | 18-month overall survival |
| [**NCT02030860**](ctgov:NCT02030860) | Pilot | 15 | Neoadjuvant gemcitabine + nab-paclitaxel +/- paricalcitol | Number of adverse events |
| [**NCT02305186**](ctgov:NCT02305186) | Randomized phase Ib/II | 56 | Neoadjuvant capecitabine-based CRT +/- pembrolizumab (MK-3745) | Safety and immune response |
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| **Abbreviations:** CRT, chemoradiation therapy; GVAX, granulocyte-macrophage colony–stimulating factor gene-transfected tumor cell vaccine; PEXG, cisplatin, epirubicin, capecitabine, gemcitabine; R0, margin-negative surgical resection. | | | | |