BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Oncology Research
https://ojs.bilpublishing.com/index.php/jor

REVIEW

Role of Radiotherapy in the Management of Pancreatic Adenocarcinoma: Debate and Discordance in Clinical Trials

Avik Mandal*

All India Institute of Medical Sciences Patna, 801505, India

ARTICLE INFO

Article history
Received: 29 August 2021
Accepted: 7 September 2021
Published Online: 13 September 2021

Keywords:
Pancreatic adenocarcinoma
Radiotherapy
Chemoradiotherapy
Clinical trials

ABSTRACT

Pancreatic adenocarcinoma (PAC) is an extremely fatal malignancy with dismal outcome with standard treatment till date. Investigators are constantly in search of optimal treatment approach and radiation therapy (RT) remains in the centre of debate. Human pancreatic cancer cell lines have shown both intrinsic and hypoxia induced radio resistance, and RT has produced conflicting results as well in the various clinical trials. However, most of the American studies continued the use of RT as a potential treatment modality but the European school of thought is widely criticized for their 'therapeutic nihilism' towards radiation and faulty clinical trial designs.

This article has reviewed the available literature on the evolving role of RT for the management of resectable and borderline resectable PAC and has highlighted the increasing trend towards the use of radiotherapy in both adjuvant and neo adjuvant settings. With the advent of modern RT techniques, the acute and late toxicities are much less than the earlier time, and therefore augmented RT is expected to produce better clinical outcomes for the patients with pancreatic carcinoma.

1. Introduction

Pancreatic adenocarcinoma (PAC) is a formidable gastrointestinal malignancy with nearly 0.49 million of new cases globally in 2020 with staggering number of deaths of 0.46 million patients [1]. It is the 7th most common cause of cancer related death and the incidence and mortality both are much higher in countries with high human development indexes [2]. Smoking, consumption of alcohol, obesity, hypercholesterolemia, diabetes are attributed as modifiable risk factors for PAC [3,4].

In a systematic analysis for the global burden of disease, Pourshams A et al. analysed dataset of 195 countries from 1990 to 2017 and found the incidence and mortality rates of PAC increased in almost all countries over the time and it is alarmingly associated with a substantial number of years of life lost [5]. Although there is a wide geographical variation, this study reported the disability-adjusted life years as nearly 9.1 million globally in 2017. Moreover, using The Surveillance, Epidemiology and End Results stat database, PAC is projected to become second cancer related death by 2030 in the United States [6].

This devastating rate of mortality and cancer burden has kept the investigators desperately motivated in search of the most effective treatment sequence for PAC and to explore multiagent chemotherapy (CT) regimen and chemoradiotherapy (CRT) as both neoadjuvant and ad-

**Corresponding Author:*
Avik Mandal,
All India Institute of Medical Sciences Patna, 801505, India;
Email: dravikmandal@gmail.com

DOI: https://doi.org/10.30564/jor.v3i2.3646

juvant settings [7,8]. In spite of that, no paradigm shifting treatment option is being established with affirmation in the span of nearly last 50 years and clinical outcome for PAC remain dismal. While radical surgery and chemotherapy are the main treatment options with curative intent, radiation therapy (RT) still remains in the centre of debate in the treatment flowchart. Conflicting data from the published clinical trials which mostly included radiotherapy with earlier techniques and obsolete dose prescriptions is the key reason behind the less acceptance of RT as a potential treatment modality.

This article has reviewed the available literature on the evolving role of RT in the management of resectable and borderline resectable PAC and has highlighted the conflicting data of the clinical trials; however there is a trend towards the increased use of radiotherapy in both adjuvant and neoadjuvant settings for the patients with PAC with excellent clinical outcome.

2. Relative Radioresistance of Pancreatic Cancer Cells

Human pancreatic cancer cells are historically considered as less responsive to external beam radiotherapy, possibly for intrinsic and hypoxia-induced radioresistance. In 1976, Courtenay et al. reported hypoxic fraction as 25% for xenografted pancreatic cancer cells, which indicates the presence of fairly large volume of hypoxic cells [9,10]. In later year, Verovski et al. investigated a panel of eight human pancreatic cell lines and mean inactivation dose was reported as high as for intrinsically radioresistant tumors like melanoma and glioblastoma [11]. In this context, the role of several hypoxic cell sensitizers, such as doranidazole, curcumin, capecitabine are being investigated both clinically and in vitro for pancreatic carcinoma [12,13].

3. Surgery is the Mainstay of Treatment

Pancreaticoduodenectomy (Whipple procedure) followed by adjuvant chemotherapy is considered as the standard of care for resectable PAC, but majority of the disease are either unresectable or borderline resectable at diagnosis. A large number of patients with apparently local disease on imaging already might have occult metastatic disease as well. Moreover, there are high proportions of local recurrences and margin positive surgical resections (R1/R2) after Whipple procedure. As a result of these worse prognostic factors, 10-year overall survival (OS) remain less than 4% for this fatal disease, even after potentially curative resection [14].

4. Evolution of Clinical Trials Involving CRT

Way back in 1958, the regression of tumor was first reported to get enhanced with addition of 5-fluorouracil (5-FU) to RT in an animal model [15]. Upon this principle of synergistic effect of 5-FU, particularly for gastrointestinal tumors, a pilot study was undertaken for the patients with locally advanced or unresectable adenocarcinoma stomach, pancreas and large bowel [16]. Each patient was treated with 900-1200 rads per week to a total tumour dose of 3500-4000 rads, 6 fractions each week along with either 5-FU or placebo. RT portal was planned to encompass the entire clinical target volume but not larger than 20 cm x 20 cm. Survival benefit was noted for all subsets with strikingly better outcome for gastric and pancreatic carcinoma.

4.1 Gastrointestinal Tumor Study Group (GITSG)

The first multicentre, randomized control trial to assess the effect of adjuvant CRT was initiated by GITSG in the United States between 1974 to 1982 [17]. This study was stopped early due to poor accrual, however, it showed a longer median survival (21.0 months vs. 10.9 months; $p < 0.05$) and better 2-year survival (43% vs. 19%) in the group treated with adjuvant CRT. An additional thirty patients were later enrolled to adjuvant CRT arm and the result still confirmed the survival benefit seen in the original study. Based on such encouraging findings, use of adjuvant CRT for PAC was started particularly in the United States.

4.2 Inferior Result with CRT in European Organisation for Research and Treatment of Cancer (EORTC) & European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial

To validate the prior results of GITSG, EORTC started randomization of 218 patients with pancreatic head carcinoma and periampullary carcinoma (between 1987 and 1995) into two groups: adjuvant CRT versus observation alone after surgery [18]. RT was delivered as 40 Gy in a split-dose schedule with concurrent continuous infusional 5-FU. No further maintenance chemotherapy was administered. Median survival and OS in adjuvant CRT arm failed to achieve any statistically significant difference.

Subsequently ESPAC-1 Trial was initiated in 11 European countries in 1994 and randomized 289 patients with resected pancreatic ductal carcinoma into 4 arms by 2x2 factorial design: CRT (n=73) or CT (n=75) neither treatment (n=69), or both treatments (n=72) [19]. Nearly half of the patient population had regional node positive disease, whereas positive margin and local invasion found during surgery were reported as 18% and 20 % respectively. RT was delivered in 40 Gy/split dose schedule along with

 DOI: https://doi.org/10.30564/jor.v3i2.3646

intravenous bolus of 5-FU in first three days of radiotherapy. CT consisted of an intravenous bolus of leucovorin, followed by an intravenous bolus of 5-FU for 5 consecutive days for six cycles. This study found adjuvant CT to produce a significant survival benefit in patients with resected PAC, whereas CRT had a deleterious effect on survival. The estimated five-year survival rate was 10 % in CRT arm, however it was 20 % among patients who did not receive CRT (P=0.05). Taken at face value, results of EORTC and ESPAC-1 study uphold the notion that adjuvant CRT should not be administered routinely for potentially resected PAC.

Counteract the inferior results

Inferior results with the administration of adjuvant CRT as demonstrated by EORTC and ESPAC-1 should be interpreted with caution and subsequent 'therapeutic nihilism' about radiotherapy should be addressed keeping the following factors in mind [20]:

a) These trials including GITSG, EORTC and ESPAC-1 used a low total dose of RT in an obsolete dose schedule. Split dose fractions are radiobiologically inferior because of the accelerated repopulation of tumor clonogens and is no longer used in current practice.

b) Non conformal techniques (AP-PA fashion) for abdominal RT would invariably result into high treatment-related toxicity and decreased survival of the patients.

c) No details of quality assurance (QA) for RT are available. Surgery, or pathological findings are not documented thoroughly.

d) Trials are underpowered and some of them included heterogeneous tumor sites. Clinical outcomes of periampulary carcinoma would be better than PAC and this might influence the overall analysis.

e) More than 20% of patients in CRT arm did not receive the intended treatment because of postoperative complications or lack of compliance in EORTC trial. Not receiving maintenance chemotherapy, unlike GITSG study might be another reason of inferior result with CRT in this particular trial.

Inferior outcome of ESPAC-1 trial has led to subsequent omission of adjuvant RT from most of the adjuvant trials in Europe, including ESPAC-3 and ESPAC-4 [21,22]. The publication of CONKO-001 (Charité Onkologie 001) trial, which was conducted from 1998 to 2004 in Germany and Austria further reduced the practice of adjuvant RT for the patients with locally advanced PAC and adjuvant gemcitabine without RT became the standard of treatment [23].

4.3 Continuing Use of CRT in the United States

American studies involving the management of PAC remained inquisitive regarding the role of radiation and GITSG trial laid the foundation for continuing use of CRT in the United States.

At Mayo clinic in Rochester, 472 patients with PAC were evaluated retrospectively who underwent R0 resection between 1975 and 2005 and 274 patients received adjuvant RT [24]. 45 Gy in 25 fractions was delivered to the tumor bed and regional nodes with a four-field technique followed by an additional 5.4 to 9 Gy boost to the tumor bed. This study reported survival benefit with adjuvant CRT (Median survival 25.2 versus 19.2 months, p=.001). Positive LN and high histologic grade were identified as adverse prognostic factors.

Despite the heterogeneous results of the randomized phase III trials, several nonrandomized, single institute US series have consistently demonstrated survival benefit with the addition of adjuvant CRT for resected pancreatic cancer. Studies conducted at Johns Hopkins University, and an analyses of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database are the examples to be mentioned with special emphasis [25,26].

In this context, Radiation Therapy Oncology Group (RTOG)/Gastrointestinal Intergroup trial 9704 was designed to compare 5-FU versus gemcitabine based CT, 3 weeks prior to CRT and 12 weeks after CRT [17,27]. CRT in both arms consisted of 50.4 Gy delivered in 28 fractions (5 days per week) with continuous 5-FU infusion (250 mg/m2/d). RT was delivered to the tumor bed and regional nodes, defined by preoperative CT imaging. Regional nodal stations particularly pancreatic, celiac, mesenteric, periaortic, duodenal, and hepatic portal lymph nodes were included in the RT fields. After an initial dose of 45 Gy, a boost dose of 5.4 Gy was delivered to the tumor bed only. This study included CRT in the both treatment arms and therefore, the independent effect of CRT cannot be assessed. However, it is the largest randomised clinical trial (RCT) that used CRT in the adjuvant settings affirming its contributing role in the management of PAC. Survival benefit at 3 years was demonstrated with the use gemcitabine, but it got disappeared on 5 years of follow up and a large percentage of distant relapse (73%) were reported [28]. Hence, any improvement in survival associated with the use of gemcitabine appears to be temporary and marginal.

These findings prompted the investigators to design a further phase III adjuvant trial to evaluate the impact of CRT after completion of a full course of gemcitabine (NRG Oncology/RTOG 0848) [29]. In the first randomization the impact of the addition of erlotinib to gemcitabine is being tested. After 5 cycles of gemcitabine based therapy, if no evidence of disease progression is found on imaging,

DOI: https://doi.org/10.30564/jor.v3i2.3646

a second randomization evaluating the impact of CRT would take place. Notable point for this trial is inclusion of 16% of patient population with histologically positive margins. Result of step 1 indicates addition of erlotinib to gemcitabine did not provide survival benefit and the answer regarding the role of adjuvant RT is still awaited.

4.4 Role of Neo Adjuvant RT

Neoadjuvant therapy is believed to produce potential advantages over upfront surgery in patients with localized PAC. With the increased possibility of R0 resection, this approach may lead to a better survival rate and is becoming more acceptable alternative over the years. Furthermore, a vast majority of the patients fail to recover sufficiently or in time after the morbid and extensive surgery leading to the omission or delay of the adjuvant treatment [30]. A meta analysis of 38 studies with the resectable or borderline resectable pancreatic cancer patients reported improved OS by intention to treat with neoadjuvant therapy, despite a drop in the resection rate [31].

The Dutch PREOPANC-1 trial compared neoadjuvant gemcitabine-based CRT to upfront surgery, followed by adjuvant gemcitabine in the both arms [32]. Although OS benefit was not demonstrated, all secondary outcomes found superiority in neoadjuvant arm. Rate of R0 resection, disease free survival, and locoregional recurrence free interval were significantly better with neoadjuvant CRT [33].

With the wide introduction of FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) in the subsequent years as a superior multiagent chemotherapy, PREOPANC-2 trial is further designed with the aim of direct comparison between total neoadjuvant FOLFIRINOX and gemcitabine based CRT [34]. The trial is actively recruiting at present and the result will definitely guide us in future to choose the best neoadjuvant protocol for resectable and borderline resectable PAC.

4.5 Role of Stereotactic Body Radiation Therapy (SBRT)

Role of SBRT is emerging for the management of PAC, since the outcome of conventional CRT is considered suboptimal. With the administration of high dose RT with extreme conformity, the effect of radiation is certainly being augmented and a plethora of clinical trials has demonstrated excellent local control with minimal acute and late toxicity [35-37]. However; the detail discussion of technical feasibility and outcome of SBRT is beyond the scope of this review.

5. Conclusions

Combined modality of treatment is now the accepted rule for the management of PAC, and the role of radiotherapy is being constantly evaluated to get optimally fit into the treatment algorithm. While the margin positive resection and pathologically positive lymph nodes are widely accepted indications for adjuvant CRT, routine use of adjuvant RT is debatable. A total dose of 45-54 Gy to the tumor bed in conventional fractionation schedule is usually accepted, but the elective nodal irradiation and the inclusion of anastomotic sites are not universally followed.

RT has demonstrated adequate efficacy to control pain and obstructive symptoms by shrinking local disease and facilitates R0 resection if administered in neoadjuvant settings. SBRT to a total dose of 30-45 Gy in 3 to 5 fractions can produce excellent local control and presently its role is under evaluation by a plethora of clinical trials. At the time of writing this article, a database of more than hundred clinical trials of SBRT in pancreatic cancer is showing with the search in https://clinicaltrials.gov/ [38]. However, extreme caution need to be taken to minimise the dose to the OARs and respiratory motion management is the another challenge to be dealt with modern radiotherapy techniques.

References

[1] *Pancreas*.; 2020. https://gco.iarc.fr/today. Accessed May 29, 2021.

[2] Huang J, Lok V, Ngai CH, et al. Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. *Gastroenterology*. 2021;160(3):744-754. DOI: 10.1053/J.GASTRO.2020.10.007.

[3] Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: Case-control study. *Am J Gastroenterol*. 2007;102(12):2696-2707. DOI: 10.1111/j.1572-0241.2007.01510.x.

[4] Alsamarrai A, Das SLM, Windsor JA, Petrov MS. Factors That Affect Risk for Pancreatic Disease in the General Population: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *Clin Gastroenterol Hepatol*. 2014;12(10):1635-1644.e5. DOI: 10.1016/j.cgh.2014.01.038.

[5] Pourshams A, Sepanlou SG, Ikuta KS, et al. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol*. 2019;4(12):934-947. DOI: 10.1016/S2468-1253(19)30347-4.

 DOI: https://doi.org/10.30564/jor.v3i2.3646

[6] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the united states. *Cancer Res*. 2014;74(11):2913-2921. DOI: 10.1158/0008-5472.CAN-14-0155.

[7] Katayama ES, Hue JJ, Bajor DL, et al. A comprehensive analysis of clinical trials in pancreatic cancer: What is coming down the pike? *Oncotarget*. 2020;11(38):3489-3501. DOI: 10.18632/oncotarget.27727.

[8] RA A, AM L, EM O, RA W, VJ P, PW P. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol*. 2009;16(7):1751-1756. DOI: 10.1245/S10434-009-0413-9.

[9] COURTENAY VD, SMITH IE, PECKHAM MJ, STEEL GG. In vitro and in vivo radiosensitivity of human tumour cells obtained from a pancreatic carcinoma xenograft. *Nat 1976 2635580*. 1976;263(5580):771-772. DOI: 10.1038/263771a0.

[10] Moulder JE, Rockwell S. Hypoxic fractions of solid tumors: Experimental techniques, methods of analysis, and a survey of existing data. *Int J Radiat Oncol Biol Phys*. 1984;10(5):695-712. DOI: 10.1016/0360-3016(84)90301-8.

[11] Verovski V, Van den Berge D, Soete G, Bols B, Storme G. Intrinsic radiosensitivity of human pancreatic tumour cells and the radiosensitising potency of the nitric oxide donor sodium nitroprusside. *Br J Cancer 1996 7411*. 1996;74(11):1734-1742. DOI: 10.1038/bjc.1996.623.

[12] Y S, T K, K K, M T. Radiosensitivity of human pancreatic cancer cells in vitro and in vivo, and the effect of a new hypoxic cell sensitizer, doranidazole. *Radiother Oncol*. 2000;56(2):265-270. DOI: 10.1016/S0167-8140(00)00181-X.

[13] Schwarz K, Dobiasch S, Nguyen L, Schilling D, Combs SE. Modification of radiosensitivity by Curcumin in human pancreatic cancer cell lines. *Sci Reports 2020 101*. 2020;10(1):1-10. DOI: 10.1038/s41598-020-60765-1.

[14] A P, P H, W H, et al. Characteristics of 10-Year Survivors of Pancreatic Ductal Adenocarcinoma. *JAMA Surg*. 2015;150(8):701-710. DOI: 10.1001/JAMASURG.2015.0668.

[15] Griesbach L, Montag Bettyj, Schnitzerande Grunberg RJ. *Studies on Fluorinated Pyrimidines II. Effects on Transplanted Tumors**.; 1958.

[16] Moertel CG, Childs DS, Reitemeier RJ, Colby MY, Holbrook MA. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. *Lancet*. 1969;2(7626):865-867. DOI: 10.1016/s0140-6736(69)92326-5.

[17] Kaiser MH, Ellenberg SS. Pancreatic Cancer: Adjuvant Combined Radiation and Chemotherapy Following Curative Resection. *Arch Surg*. 1985;120(8):899-903. DOI: 10.1001/archsurg.1985.01390320023003.

[18] 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. In: *Annals of Surgery*. Vol 230. Lippincott, Williams, and Wilkins; 1999:776-784. DOI: 10.1097/00000658-199912000-00006.

[19] 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.

[20] Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. *Int J Radiat Oncol Biol Phys*. 2005;61(4):965-966. DOI: 10.1016/j.ijrobp.2004.11.018.

[21] Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: A randomized controlled trial. *JAMA - J Am Med Assoc*. 2010;304(10):1073-1081. doi:10.1001/jama.2010.1275

[22] Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389(10073):1011-1024. DOI: 10.1016/S0140-6736(16)32409-6.

[23] 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. *J Am Med Assoc*. 2007;297(3):267-277. DOI: 10.1001/jama.297.3.267.

[24] Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: The Mayo Clinic experience (1975-2005). *J Clin Oncol*. 2008;26(21):3511-3516. DOI: 10.1200/JCO.2007.15.8782.

[25] Yeo CJ, Abrams RA, Grochow LB, et al. Pancreati-

  DOI: https://doi.org/10.30564/jor.v3i2.3646

coduodenectomy for pancreatic adenocarcinoma: Postoperative adjuvant chemoradiation improves survival: A prospective, single-institution experience. *Ann Surg*. 1997;225(5):621-636.
DOI: 10.1097/00000658-199705000-00018.

[26] Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: A population-based, linked database analysis of 396 patients. *Ann Surg*. 2003;237(1):74-85.
DOI: 10.1097/00000658-200301000-00011.

[27] 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 - J Am Med Assoc*. 2008;299(9):1019-1026.
DOI: 10.1001/jama.299.9.1019.

[28] Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol*. 2011;18(5):1319-1326.
DOI: 10.1245/s10434-011-1630-6.

[29] Abrams RA, Winter KA, Safran H, et al. Results of the NRG Oncology/RTOG 0848 Adjuvant Chemotherapy Question-Erlotinib+Gemcitabine for Resected Cancer of the Pancreatic Head: A Phase II Randomized Clinical Trial. *Am J Clin Oncol Cancer Clin Trials*. 2020;43(3):173-179.
DOI: 10.1097/COC.0000000000000633.

[30] RP M, KY B, JS T, et al. Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg*. 2014;260(2):372-377.
DOI: 10.1097/SLA.0000000000000378.

[31] Versteijne E, Group on behalf of the DPC, Vogel JA, et al. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg*. 2018;105(8):946-958.
DOI: 10.1002/BJS.10870.

[32] E V, CH van E, CJ P, et al. Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC trial): study protocol for a multicentre randomized controlled trial. *Trials*. 2016;17(1).
DOI: 10.1186/S13063-016-1262-Z.

[33] E V, M S, K G, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol*. 2020;38(16):1763-1773.
DOI: 10.1200/JCO.19.02274.

[34] Janssen QP, van Dam JL, Bonsing BA, et al. Total neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2 trial): study protocol for a nationwide multicenter randomized controlled trial. *BMC Cancer 2021 211*. 2021;21(1):1-8.
DOI: 10.1186/S12885-021-08031-Z.

[35] Suker M, Nuyttens JJ, Eskens FALM, et al. Efficacy and feasibility of stereotactic radiotherapy after folfirinox in patients with locally advanced pancreatic cancer (LAPC-1 trial). *EClinicalMedicine*. 2019;17:100200.
DOI: 10.1016/J.ECLINM.2019.10.013.

[36] Cohen DJ, Medina B, Du KL, et al. Phase II multi-institutional study of nivolumab (Nivo), cabiralizumab (Cabira), and stereotactic body radiotherapy (SBRT) for locally advanced unresectable pancreatic cancer (LAUPC). *https://doi.org/101200/JCO20193715_supplTPS4163*. 2019;37(15_suppl):TPS4163-TPS4163.
DOI: 10.1200/JCO.2019.37.15_SUPPL.TPS4163.

[37] Oar A, Lee M, Le H, et al. AGITG MASTERPLAN: a randomised phase II study of modified FOLFIRINOX alone or in combination with stereotactic body radiotherapy for patients with high-risk and locally advanced pancreatic cancer. *BMC Cancer 2021 211*. 2021;21(1):1-11.
DOI: 10.1186/S12885-021-08666-Y.

[38] Search of: SBRT | Pancreatic Cancer - List Results - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/results?cond=Pancreatic+Cancer&term=SBRT&cntry=&state=&city=&dist=. Accessed August 30, 2021.

 DOI: https://doi.org/10.30564/jor.v3i2.3646