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REVIEW ARTICLE

The Role of Neoadjuvant and Adjuvant Chemotherapy in Pancreatic Cancer

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Abstract

Pancreatic cancer is an aggressive malignancy. Recurrences are very high despite high-quality surgery necessitating adjuvant therapy. The evolution of adjuvant therapy took several decades and gradually evolved from single-agent chemotherapy to multi-agent chemotherapy. The two important agents that are active in pancreatic cancer are 5-fluorouracil and gemcitabine, and with several combinations showing better results in the subsequent trials, the most recent trial PRODIGE 24 shows a median survival of 54.4 months. The role of neoadjuvant therapy is still evolving in resectable cancers. The role of adjuvant radiotherapy is not well defined due to controversial results from historical trials.

Keywords Pancreatic cancer · Adjuvant chemotherapy · Resectability · Neoadjuvant chemotherapy · Adjuvant radiotherapy

Key Points

- Pancreatic cancer is a highly aggressive disease in all stages, and cumulative 5-year survival is 8%.
- The multi-detector contrast-enhanced CT scan with pancreatic protocol is the standard of imaging for determining resectability.
- There are 3 subsets of non-metastatic pancreatic cancer that can be defined by using the resection criteria: resectable, borderline resectable, and locally advanced pancreatic cancers.
- The role of neoadjuvant therapy in resectable pancreatic cancer is still evolving, and the upfront resection with adjuvant chemotherapy is the standard of care.
- Surgery is the most important modality determining curability.
- Adjuvant chemotherapy in all stages of resected pancreatic cancer increases the survival rate and decreases recurrence rates.
- Age is no bar for fit patients while considering adjuvant therapy and comprehensive geriatric assessment should be considered to determine the fitness for regimen whenever possible.
- The standard adjuvant regimen in fit patients is modified FOLFIRINOX, and the completion of 6 months of planned adjuvant treatment is an independent factor for survival.
- Adjuvant chemotherapy should be started within 8 weeks of surgery provided complete recovery after surgery.

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Pancreatic Cancer: Biology and Prognosis

Pancreatic ductal adenocarcinoma is inherently aggressive in biological behavior and is resistant to most available treatments, an important reason for shorter 5-year survival overall up to 8% cumulative for all stages including the early stages treated with curative intent [1]. It is expected to become the second most common cause of cancer-related mortality in the next 10 years in the Western population [2].

Recognizing pancreatic cancer at the resectable stage is the most important prognostic factor; however, the role of systemic therapy is becoming more and more prominent with the recognition of the systemic biological nature of pancreatic cancer at onset, although the clinical decisions of resection and adjuvant treatment and intent of treatment are based on radiologically available data and characteristics of patient at presentation including comorbidities and performance status [3].

Criteria for Resection

The most important decision of the possibility of resections has been revised and improvised over time, and a consensus has been achieved and uniformly followed across the globe. Three important societies that played a key role in the development of these criteria are the Society of Surgery for Alimentary Tract, The American Hepato Pancreatic Biliary Association, and the Society of Surgical Oncology.

The National Comprehensive Network further revised the Resectability criteria [4].

Important features of the criteria are as follows:

- The imaging of choice to assess resectability is cross-sectional imaging with multidetector contrast-enhanced computed tomography (CT) scan with multiphase dynamic contrast, pancreatic protocol [5].
- The involvement of 3 critical vessels adjacent to the pancreas by pancreatic tumor is considered. These are the superior mesenteric artery (SMA), superior mesenteric vein (SMV), and celiac axis [6].
- The absence of involvement of these vessels by pancreatic tumour is suggestive of clear resectability.

Very few patients up to less than 20% of all pancreatic cancers are present in the stage of resectability. About 10% of patients present in the stage of borderline resectability, which is defined by anatomical, as well as conditional and biological factors that may predict the possibility of positive tumor margins or poor post-surgical outcomes if operated upfront [7].

- Borderline resectability is defined concerning arteries among the critical vascular structures mentioned above, i.e., celiac artery and SMA, that the contact of the tumour should be less than 180° of the semi-circumference of the vessel, defined as an abutment, and there should be no stenosis or deformity of the vessel identifiable on imaging.
- To venous critical structures SMV and or portal vein, borderline resectability is defined as a pancreatic tumor causing distortion occlusion or narrowing of the vessel with the technical feasibility of safe resection and reconstruction.
- Apart from these anatomically defined characteristics on cross-sectional imaging, biological factors such as high serum tumor marker levels, defined as high carbohydrate antigen 19–9 levels more than 500 KU/L and patient's characteristic of Eastern Cooperative Oncology Group (ECOG) Performance status 2 or more are defined as borderline resectable features.
- All the other tumors extending beyond these features without metastases are defined as locally advanced pancreatic cancers and when spread to non-regional lymph nodes or other organs are considered metastatic stage.
- Any patient not undergoing or planned for surgery is essentially treated with palliative intent.

Factors to be considered before planning definitive therapy [8]:

- Performance status and nutritional status of the patient.
- End organ function to determine the chemotherapy regimen.
- Resectability status as assessed by the surgical team or MDT.
- To rule out metastatic disease.

The imaging modality of choice for staging is a contrast-enhanced CT scan of the chest and abdomen. However, multidetector CT scans can underestimate metastatic disease in up to 20% of cases [9].

In suspected liver metastases on CT scan, it is preferable to perform a contrast-enhanced triple-phase MRI scan to determine the exact number of Liver metastases, as the sensitivity is high [10].

In patients with symptoms suggestive of distant metastases or tumor marker CA19-9 elevations of more than 10,000 IU/L, it is preferable to do PET CT to rule out distant disease and so to avoid futile surgical explorations [11].

Role of Neoadjuvant Chemotherapy in Resectable Cancers

The rationale for using chemotherapy in upfront resectable pancreatic cancer:

- Pancreatic cancer is a systemic disease to start with, and systemic therapy may address and eradicate the micrometastatic disease, and possibility of R0 resection will increase which in turn is associated with increased survival.
- Better selection of patients for surgery and understanding of the biological behavior of pancreatic cancer in particular individuals. The cancers which have progressed on neoadjuvant therapy might not benefit from surgery.
- Higher chances of R0 resection.
- Definitive chance of delivering systemic therapy, as nearly one-fourth of patient's post-surgery may not recover enough to receive systemic therapy [12].

However, the most important challenge in planning neoadjuvant chemotherapy in aggressive pancreatic cancers is that approximately more than half of the patients started on neoadjuvant therapy may not be able to undergo surgery due to clinical decline in performance status and progression of the disease [13]. Various oncology societies like ESMO and NCCN have given suggestions on the use of neoadjuvant therapy in high-risk resectable pancreatic cancer, albeit not defining the exact criteria of high-risk disease. Some of the high-risk factors defined by ASCO and NCCN are high CA19-9 > 1000 U/ml large primary tumours, large lymph nodes, severe pain, weight loss, etc.

Establishing the histopathological diagnosis before planning neoadjuvant therapy is mandatory. In patients with obstructive jaundice, biliary drainage is required to give adequate doses of planned chemotherapy. In patients with

bilirubin level more than 1.5 times elevation, biliary drainage should be done, and chemotherapy should be attempted after adequate biliary drainage from the common biliary duct. The chemotherapy in those with bilirubin, more than 1.5 times than the upper normal limit, should be started with low-dose single-agent gemcitabine, and second agent may be added later after adequate biliary drainage.

Even in those patients with normal bilirubin, with ECOG performance status of 2 or more, or with comorbidities making them non-fit for aggressive chemotherapy, single-agent gemcitabine should be started, after clear discussion with the patient about the reduced response rates than the intensive chemotherapy. The option in young, fit patient with comorbidities is FOLFIRINOX regimen, and in those who are not fit for triple agent chemotherapy should be offered FOLFOX regimen or a combination of gemcitabine with nab paclitaxel. In all patients diagnosed with pancreatic adenocarcinoma, in those who are planned for neoadjuvant chemotherapy should be offered genetic testing for homologous recombination repair gene mutation in tissue (somatic) and germline testing (blood).

Neoadjuvant Treatment Modalities

Combination of Chemotherapy and Radiotherapy

Phase III data on these modalities in a neoadjuvant setting is not available. Most of the data is from phase II studies and retrospective data. Two regimens are widely used in these trials. The first regimen is 5-FU, oxaliplatin, irinotecan, and leucovorin (FOLFIRINOX) followed by 5-FU-based CTRT, and the second regimen is gemcitabine-based concurrent chemoradiotherapy [14]. The possible reason for the high rates of R0 resection shown in these trials as compared to the upfront surgery strategy in the historical data may be due to the high margin positivity rates with the upfront surgical strategy leading to poor survival rates. The upfront gemcitabine-based CTRT strategy was studied in the PREOPANC trial, which showed that OS rates are not superior to the upfront surgery strategy [15].

Neoadjuvant Chemotherapy

NEONAX is a phase II trial comparing chemotherapy with gemcitabine and nab paclitaxel in peri-operative and post-operative settings. The differences in disease-free survival and the primary endpoint were not met. However, more than 90% of patients in the peri-operative arm were exposed to chemotherapy whereas less than half in the post-operative arm were exposed to chemotherapy [16]. In another Japanese study, comparing gemcitabine and S1 in a pre-operative setting versus upfront surgery, it was shown that survival is significantly higher in those receiving pre-operative chemotherapy [17].

To determine the optimal regimen for pre-operative therapy, the SWOG S1505 study has compared two regimens with different mechanisms of activity, and toxicities, i.e., FOLFIRINOX and gemcitabine-nab paclitaxel. However, this trial has failed to show the superiority of one regimen over the other, as both have an equal pathological response, 2-year overall survival, and both failed to achieve the primary endpoint of 2-year survival of 58% landmark [18].

Role of Neoadjuvant Chemotherapy in Borderline Resectable Pancreatic Cancers

There is a high probability of incomplete resection in borderline pancreatic cancers. All such cases should be discussed in multidisciplinary tumour board meetings, and a decision should be taken. The role of neoadjuvant treatment in borderline resectable cancers is still in evolution. All borderline, locally advanced, and advanced pancreatic cancers should be assessed for the presence of germline or somatic mutations in BRCA1 and 2 or similar genes. Around 10% of all pancreatic cancers harbor such mutations, out of which half of the mutations are somatic (tested on tumor tissue) and half are germline (tested in blood). Cancers that are positive for these alterations are sensitive to platinum agents. With extrapolation of the data from breast and ovarian cancers, it seems that platinum regimens work better in these cancers with alterations, and NCCN guidelines recommend either FOLFIRINOX (oxaliplatin-containing regimen) or gemcitabine-cisplatin regimen in these cancers as preferred regimens. In those without alterations or in those without the test results of these alterations, the preferred regimens are FOLFIRINOX or gemcitabine and nab-paclitaxel. Patients should be in ECOG PS0 or 1 to be able to receive FOLFIRINOX. The common clinical protocol is included in Tables 1 and 2.

Re-evaluation after neoadjuvant chemotherapy should be done clinically after every cycle, and radiological evaluation should be done after 2 months and 4 months. If a patient is fit for surgery, surgical referral should be done and, in case of decline in performance status, should be discussed in multidisciplinary tumor board for the consideration of radiotherapy in select patients. In those cases which are unresectable, or those who developed distant metastases, palliative chemotherapy is the option.

Table 1 Patient chosen for surgery (early-stage pancreatic cancer)

Patient chosen for Surgery (Early-Stage Pancreatic Cancer)

Staging evaluation in proven Pancreatic cancer

⇩

ECOG PS0 or 1

Fit for Major surgery.

Normal End Organ Functions

⇩

Upfront Surgery Done

⇩

pT1No or higher

⇩

Adjuvant chemotherapy +/- CTRT

Table 2 Patient chosen for neoadjuvant chemotherapy (early-stage pancreatic cancer)

Patient chosen for Neoadjuvant Chemotherapy (Early-Stage Pancreatic Cancer)

Staging evaluation in proven Pancreatic cancer

HRR Somatic and Germline testing

⇩

ECOG PS0

Fit for Triplet chemotherapy.

Normal End Organ Functions

⇩

FOLFIRINOX

⇩

in all other patients → Folfox or Gemcitabine - Nab paclitaxel

⇩

Re-evaluation every 2 months

Role of Adjuvant Chemotherapy

Evolution of Adjuvant Chemotherapy

Despite the best possible resection, nearly 80% of all patients recur without adjuvant therapy. The adjuvant therapy took several decades to evolve to the current standard and is still in the process of searching for a better regimen. The first trial testing observation after surgery versus 5-fluorouracil-based chemoradiotherapy followed by chemotherapy has been prematurely terminated because of large differences of benefit observed with chemotherapy compared to observation (DFS 20 months versus 11 months in the observation) [19]. ESPAC-1 is the next step in the evolution; in a trial with 4 arms, 2 of the important arms are adjuvant chemotherapy and chemoradiotherapy followed by maintenance therapy. The chemotherapy used in the trial was 5-FU day 1 to day 5 every 28 days for 6 months. From this trial, it is concluded that adjuvant chemotherapy should be considered as standard of care and adjuvant CTRT seems to deliver an inferior outcome. However, it should be noted that the type of radiation then employed in the trial was very crude compared to newer techniques available now [20].

The first attempt of comparing 5-FU and gemcitabine-based regimens was attempted by the ESPAC-3 trial. The regimens used were Mayo's 5-FU protocol used at 425 mg/m^2 IV bolus day 1 to day 5 preceded by IV folinic acid 20 mg/m^2 every 28 days and single-agent gemcitabine at the dose of 1000 mg/m^2 on day 1.8.15 every 28 days. The difference between the two arms was not significant; however, this brought the newer gemcitabine into light, which is easy to deliver to patients and has a favorable toxicity profile. Grade 3 or 4 stomatitis and diarrhea were mostly seen in the 5-FU arm, while more grade 3 hematological toxicities were seen in the gemcitabine arm. This also proves an important point that both 5-FU and gemcitabine are active agents that could improve outcomes in pancreatic cancer, and so, the next trial ESPAC 4 was designed with a combination of both the agents [21]. ESPAC 4 trial compared the combination of gemcitabine and capecitabine with gemcitabine, and it was shown that the combination prolongs median overall survival up to 30.2 months compared to 27.9 months with gemcitabine alone. S1, a 5-FU analog extensively used in Japan, in adjuvant JASPAC trial has shown that the survival is prolonged up to 46.5 months as compared to 25.5 months with gemcitabine alone. S1 has not been approved by the FDA, quoting the differences in the pharmacodynamics in the West versus the Japanese population. However, S1 is an approved molecule by the European Medical Association [22].

The most recent and effective regimen evolved from the PRODIGE24 study is modified FOLIFIRINOX, a regimen adopted from a metastatic setting, and bolus 5-FU is avoided. This trial included a patient population with excellent performance status only, and hence in the clinical settings, patient selection is very important. The median survival with regimen in 54.4 months, however, was associated with higher grade 3 and 4 adverse events [23].

In those who have received neoadjuvant chemotherapy, it is suggested to complete 6 months of total peri-operative therapy, although there is no phase III data to suggest the same.

Role of Adjuvant Radiotherapy

The role of postoperative radiation is not well defined due to several contradictory results in the historical trials. American Society recommends the use of radiotherapy in positive margin status and positive lymph nodal status. European society has not recommended radiotherapy in adjuvant settings.

The role of adjuvant RT has always been unclear in adjuvant settings after resection in pancreatic cancer. There is limited data, and within the data available, there are contradictory results. The results of the historical trials garnered much criticism due to suboptimal doses of radiotherapy used, heterogeneous methodologies employed, variations in concurrent chemotherapy regimens, and flaws in the methods of analysis. As of now, the American Society of Clinical Oncology recommends radiation in adjuvant settings only for positive lymph nodal status or positive margins. European guidelines do not support the use of radiation in any setting after resection of pancreatic cancer.

Future Perspectives

Despite the better understanding of molecular biology in this decade, there are no monumental developments that changed the course of pancreatic cancer treatment. There are attempts to improve treatments by a multi-pronged approach. The first modality is the development of better drugs and regimens. Such an attempt is the development of a new drug liposomal irinotecan combining with 5-fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX). The phase III trial NAPOLI 3 testing NALIRIFOX against gemcitabine and nab paclitaxel has shown better overall survival and progression-free survival, which led to the approval of this regimen by the FDA in June 2023 as a supplemental new drug application of NALIRIFOX as a frontline regimen for pancreatic cancer [24]. The second approach is an attempt to increase drug sensitivity to proven drugs like gemcitabine. A French group of scientists attempted non-viral gene transfer of deoxycytidine kinase and uridine monophosphate kinase to improve

the sensitivity to gemcitabine without increasing the toxicity [25]. There is an increased interest in targeting the stromal component of pancreatic tumor, in which a glycoprotein SPARC (secreted protein acidic and rich in cysteine) appears to play a central role, which is also referred to as osteonectin or BM-40. Overexpression of SPARC seems to be responsible for increased invasive capacity and poorer prognosis. SPARC protein seems to have increased affinity for albumin, and so, nano-albumin-paclitaxel seems to be more efficacious in this tumor [26]. In the same process of targeting stroma, fibroblast activating tumor inhibitor theragnostic approach is being studied in pancreatic cancer [27]. The third approach is to synthesize personalized cancer vaccines using neoantigens from patients' tumors to trigger an immune response in combination with checkpoint inhibitors. Pfizer-BioNTech has made the first attempt in developing such mRNA neoantigen vaccine called autogenecevureman and is currently in phase II trials [28].

Data Availability All our data is available in the quoted references. We can provide the data whenever requested from the same.

Declarations

Conflict of Interest The authors declare no competing interests.

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