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Chapter

Advances in the Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer is an aggressive solid organ malignancy with a high mortality rate. There has only been significant improvement in the overall survival until the last 5–10 years. The current trend toward the neoadjuvant approach of pancreatic cancer has shown success in tumor response, resection rate, and even overall survival. Using dedicated pancreatic protocol cross-sectional imaging, one can now follow the tumor and pancreatic parenchyma interface as well as tumor markers to predict treatment response. Aggressive combination chemotherapy regimens such as FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan), appropriate patient selection, and multidisciplinary treatment teams have made an impact in the current management of pancreatic cancer. Surgical intervention is still the mainstay treatment of pancreatic cancer. The role of routine radiation therapy is still unknown but may benefit in situations with positive margins.

Keywords: pancreatic cancer, neoadjuvant chemotherapy, FOLFIRINOX

1. Introduction

1.1 Incidence and mortality

Pancreatic cancer is the 13th most common malignancy worldwide, which was diagnosed in approximately 338,000 people in 2012. Pancreatic cancer is a very aggressive form of malignancy resulting in the seventh leading cause of cancer deaths worldwide, over 331,000 deaths in 2012 alone. The worldwide incidence of new pancreatic cancers was 4.9 in 100,000 persons with an associated mortality rate of approximately 4%. The incidence and deaths of pancreatic cancer is higher in developed countries, 188,000 and 184,000 persons as compared to less developed regions, 150,000 and 146,000 persons [1].

Specifically looking at the USA, pancreatic cancer is the eighth most common type of malignancy and the fourth leading cause of cancer deaths. There are estimated 55,440 new cases of pancreatic cancer that will be diagnosed in the USA in 2018 and result in estimated 44,330 deaths. Incidence rate of pancreatic cancer has increased 1% per year from 2005 to 2014 [2].

Most pancreatic cancers develop from the pancreatic exocrine tissue (94%), such as invasive ductal adenocarcinoma, while the remaining 6% of tumors stem from the hormone-producing islet cells, such as insulinomas, gastrinomas, and other pancreatic neuroendocrine tumors (pNETs). Those pNets will typically occur in younger patients with a better overall prognosis. The focus of this chapter will be on invasive pancreatic ductal adenocarcinoma [2].

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The overall pancreatic cancer mortality rate has shown only slight improvement over the past 35 years. In 1975, pancreatic cancer mortality rate was observed at 3.1%, and in 2000, it increased to 5.2%. The largest incremental improvement in pancreatic cancer survival has occurred over the past 10 years (2008–2104), with the all stage 5 year survival between 8 and 8.5% [2–4].

For the small percentage of patients with early-stage localized pancreatic cancer (10%), the 5-year survival is between 32 and 34.3%. Once regional lymph node involvement has developed, the 5 year survival decreases to 11.5–12%. Unfortunately, most pancreatic cancer patients (52%) are diagnosed with distant metastatic disease, and that 5-year survival is only 3% [2, 3].

1.2 Risk factors

At this point in the time, the cause of pancreatic cancer is still unknown. Increasing age is a significant risk factor for developing pancreatic cancer. The median age of diagnosis of pancreatic cancer in both sexes is at 70 years old. In addition, men have an increased incidence of developing pancreatic cancer as compared to women, 14.4 vs. 11.2 per 100,000 persons across all race and ethnicity [1–3].

There have been several risk factors to develop pancreatic cancer associated with race/ethnicity, environmental, dietary, medical, and genetic exposures identified (**Table 1**). Race is also another significant risk factor. African-Americans have the highest incidence (9.9 per 100,000 persons) and mortality (9.4 per 100,000 persons) of pancreatic cancer as compared to non-African-Americans [4]. In addition, Jews of Ashkenazi heritage also have an increased incidence of pancreatic cancer. The age standardized incidence rate of pancreatic cancer for Israeli Jews (7.2 per 100,000 males and 5.7 per 100,000 females) exceeds the incidence of Israeli non-Jews (4.0 per 100,000 males and 2.9 per 100,000 females) [5].

There are also several hereditary conditions associated with increased risk for pancreatic cancer (**Table 2**). While persons with these genetic syndromes are at increased risk for pancreatic cancer, they only account for 5% of all pancreatic diagnoses. Familial cases of pancreatic cancer are at increased incidence to develop secondary primary cancers as compared to non-familial-based cancers. Of those listed, Peutz-Jeghers and hereditary pancreatitis syndromes have the highest risk of developing pancreatic cancer [6–12].

Environmental	Race	Medical	Dietary
Cigarette smoking Second-hand smoke Alcohol Asbestos Pesticides Herbicides Residential Radon Coal Products Welding Products Radiation	African-American Ashkenazi Jews	Pancreatitis Diabetes *Helicobacter pylori* infection Cirrhosis	High saturated fat diet Nitrosamines Overweight Obesity

Table 1.
Risk factors for developing pancreatic cancer.

Genetic Syndrome	Gene Mutation	Relative Risk
Hereditary Pancreatitis	PRSS1 (7q35)	50-80 times
Hereditary Nonpolyposis Colorectal Cancer (HNPCC, Lynch Syndrome)	hMSH2; hMLH1; hPMS2; hMSH6	Not defined
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)	BRCA2 (13q12)	10 times
Familial Adenomatous Polyposis (FAP)	APC (5q21)	5 times
Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome	P16(9p21)	20-34 times
Peutz-Jeghers Syndrome	STK11/LKB1 (19p13)	132 times
Ataxia-telangiectasia	ATM (11q22-23)	Not defined

Table 2.
Genetic syndromes with increased risk of pancreatic cancer.

Tobacco use is the most well-established modifiable risk factor for developing pancreatic cancer and accounts for up to 30% of all pancreatic cancer cases. There is at least a twofold increase in risk for developing pancreatic cancer in cigarette smoker than a non-smoker. The risk also increases with an increase in the number of cigarettes and duration of smoking. It may take up to 20 years after cessation of cigarette smoking for one's risk of pancreatic cancer to be equal to take of a non-smoker [13].

2. Treatment of resectable disease

2.1 Imaging considerations

The current standard in pancreatic cancer staging is by use of a 64-slice multidetector computed tomography (CT). Specific CT pancreatic protocols can accurately stage the cancer and assess for resectability. These protocols include both the use of low-density oral contrast and nonionic iodinated contrast and scanned 30–45 seconds then again 60 seconds after injection to capture both arterial and

venous phases. The arterial phase will allow for good visualization of the celiac axis, common hepatic artery, superior mesenteric artery, and gastroduodenal artery. The venous phase will show enhanced visualization of the portal vein, superior mesenteric vein, splenic vein, pancreatic parenchyma, and the liver to assess for metastatic disease [14, 15].

2.2 Surgical considerations

Only 20% of patients who present with pancreatic cancer can undergo surgical resection since most patients present with either unresectable or metastatic disease. The only chance for a curative treatment is with the inclusion of successful surgical removal of the cancer. To determine the patient's eligibility for pancreatic resection, an experienced pancreatic surgeon is required to review the dedicated pancreatic cross-sectional imaging. The relationship of the tumor to the major intra-abdominal vessels determines the resectability of the pancreatic cancer. Decisions regarding diagnostic and management and resectability should involve multidisciplinary consultation at high-volume center, at least 15–20 pancreatic resections per year [14].

In 2006, the National Comprehensive Cancer Network (NCCN) criteria initially defined pancreatic cancers resectability status into three classifications: resectable, borderline resectable, and unresectable. Since that time, there have been several varying definitions of tumor resectability that have evolved over the past decade. Several international surgical societies such as the American Hepato-Pancreatico-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), Society for Surgery of the Alimentary Tract (SSAT), and International Association of Pancreatology (IAP) have issued consensus statements on the definition and criteria of resectability and borderline resectable pancreatic cancers as illustrated in **Table 3** [14–16].

For a tumor to be considered resectable, it must not be in contact with the portal vein (PV) or superior mesenteric vein (SMV) per AHPBA/SSO/SSAT and IAP or less than 180° of contact with SMV/PV by NCCN criteria. By meeting these criteria, the surgeon believes there is a high likelihood of removing the cancer without leaving behind any residual tumor (R0 resection). When pancreatic cancers are classified as borderline resectable based on the vascular involvement, it means that there is a higher likelihood of having residual microscopic disease (R1 resection) if one was to proceed with upfront surgery. Borderline resectable means just that it is not quite resectable but not completely unresectable either. The criteria are less than 180° of arterial involvement of the superior mesenteric artery (SMA) or common hepatic artery (CHA) of celiac axis (CA). It also means there can be greater than 180° of involvement of SMV or even complete encasement of SMV or PV but still suitable for resection vascular reconstruction. Unresectable disease has greater than 180° of arterial involvement of SMA, CHA, or CA or non-reconstructable vein involvement including the first jejunal branch [14–16].

The best outcomes come from margin negative surgical resection with no residual microscopic disease (R0). There is current debate at the true definition of R1 resection as either no microscopic tumor cells at the resection margin or if tumor cells are less than 1 mm from the resection margin. It has been found that the 5-year survival rate has been improved in patients with greater than 1 mm of clearance as compared to those with less than 1 mm. Margins with 0 mm, less than 1 mm, or greater than 1 mm had 5-year survival rates at 16.3, 12.4, and 27.6%, respectively [17]. There is no benefit to performing a surgical resection if gross tumor (R2 resection) will be the result as the prognosis is similar to patients with non-operative management [18].

	NCCN	AHPBA/ SSO/ SSAT	IAP
Resectable Vein Artery	No tumor contact with SMV and PV or <180^o contact without vein contour irregularity	No SMV and PV abutment, distortion, tumor thrombus or venous encasement	No tumor contact or narrowing to SMV or PV
	No artery tumor contact of CA, SMA, or CHA	Clear fat planes around CA, SMA and CHA	No tumor contact to SMA, CA, CHA
Borderline Resectable Vein Artery	Tumor contact of SMV/PV > 180^o or contact <180^o resulting in vein irregularity or thrombus but with suitable proximal and distal vessel for safe resection and reconstruction Tumor contact to inferior vena cava	Abutment with or without impingement of SMV or PV lumen, short segment occlusion or encasement but with suitable vessel distal and proximal to allow for safe resection and reconstruction	Tumor contact >180^o without deformity of SMV or PV
	Head/Uncinate: Contact CHA without extension to CA Tumor contact <180^o of SMA Tumor contact with variant anatomy Tumor contact <180^o CA **Body/Tail:** Tumor contact with CA >180^o w/o involvement of aorta and intact GDA	GDA encasement w either short encasement of direct abutment of CHA without extension to CA Tumor abutment of SMA not to exceed 180^o degrees circumference of vessel wall	Tumor contact < 180^o without deformity/stenosis of SMA, CA, CHA
Unresectable Vein Artery	Unreconstructible SMV/PV due to tumor involvement or occlusion Contact with first jejunal branch into SMV		Bilateral narrowing/ occlusion beyond inferior border of duodenum
	Head/Uncinate: Tumor contact w SMA >180^o Tumor contact with CA. 180^o **Body/Tail:** Tumor contact >180^o SMA or CA Tumor contact with CHA >180^o		Tumor contact or invasion of the aorta

Table 3.
Definitions and criteria of resectable, borderline resectable and unresectable pancreatic cancer.

Pancreatic surgery should involve high-volume surgeons with the expertise in pancreatic resection. Decisions regarding the management of pancreatic cancer patients require a multidisciplinary team. The location of the tumor and extent of disease will dictate the surgical approaches. Pancreatic head and uncinate tumors require pancreaticoduodenectomy (Whipple procedure) with reconstruction of the pancreas, bile duct, and stomach. If possible, the aim is to preserve the pylorus to limit bile acid reflux and gastric emptying. Tumors that exist in the body and tail of the pancreas will typically require a left-sided surgical resection, distal pancreatectomy, and splenectomy. Borderline resectable and locally advanced cancers may also require venous and/or arterial reconstruction at the time of surgical resection of the pancreatic cancer.

2.3 Chemotherapy

In patients with pancreatic cancer, the overall survival has improved due to systemic chemotherapy and combination therapies. It is still standard treatment to perform upfront surgical resection for resectable pancreatic cancer followed by adjuvant chemotherapy. However, there has been a shift toward upfront neoadjuvant chemotherapy in order to select out patients with latent metastatic disease or to downstage borderline and locally advanced cancers.

The ESPAC-1 (European Study Group for Pancreatic Cancer) showed that there was improvement in overall survival using surgery plus adjuvant 5-fluorouracil (5-FU) plus folinic acid (FA). This three-tracked trial compared patients treated with chemotherapy alone, surgical resection alone, or chemotherapy plus radiation therapy. The highest 5-year survival was seen in the chemotherapy arm 21% as compared to surgery alone 8% and chemoradiation 11%. This revealed the only significant survival benefit was with adjuvant chemotherapy [19].

The Charite Onkologie study (CONKO-001) from 2007 compared adjuvant gemcitabine therapy to observation in patients undergoing surgical resection of pancreatic cancer. In the treatment arm, patients received 6 cycles of adjuvant gemcitabine. Patients treated with adjuvant gemcitabine vs. surgery alone had statistically significant increased median overall survival of 22.8 months and 5-year survival of 21% compared to 20.2 months and 5-year survival of 9%. Gemcitabine also significantly delayed the development of recurrent disease as compared to observation alone [20].

The ESPAC-3 was a large randomized controlled trial which compared adjuvant 5-FU plus leucovorin or gemcitabine in patients who underwent RO or R1 resection of pancreatic cancer. This was initially a three-arm study comparing 5-FU plus leucovorin, gemcitabine, and observation; however, once the results of the ESPAC-1 were available, the observation arm was closed. Results of ESPAC-1, ESPAC-1 plus, and ESPAC-3 in subset analysis of 5-FU/FA vs. observation confirmed that adjuvant 5-FU/FA had superior overall survival as compared to observation after surgical resection. The 5 year survival for 5-FU/FA was 24% compared to observation which was 14% [21].

ESPAC-3 has enrolled 1088 patients and they were followed for over 6.5 years. Median survival for gemcitabine arm was 23.6 months while 5FU/leucovorin arm was 23 months [22]. This had shown that adjuvant gemcitabine had similar survival but less toxicity as compared to 5FU. At this point, there were now two different adjuvant treatment options for resected pancreatic cancer.

Van Hoof et al. (2013) performed a phase III trial in which metastatic pancreatic cancer patients were randomized to treatment with either nab-paclitaxel (125 mg per square meter of body surface area) plus gemcitabine (1000 mg per square meter) on days 1, 8, and 15 every 4 weeks or gemcitabine monotherapy

(1000 mg per square meter) weekly for 7 of 8 weeks and then on days 1, 8, and 15 every 4 weeks. The overall survival in the nab-paclitaxel-gemcitabine was 8.5 months as compared to gemcitabine alone with 6.7 months ($p > 0.001$). This doublet therapy did result in higher rates of myelosuppression and peripheral neuropathy than gemcitabine alone [23]. While this study was based on patients with metastatic disease, it advanced the adjuvant combined chemotherapy regimen in resected pancreatic cancer.

The ESPAC-4 went on to compare adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer. Capecitabine is an orally active fluoropyrimidine carbamate which can provide prolonged fluorouracil exposure at lower peak concentrations. The 5-year overall survival with gemcitabine and capecitabine compared to gemcitabine alone was 29% vs. 16% [24]. The new standard of care quickly adopted doublet therapy as the new standard of care.

The use of adjuvant FOLFIRINOX [fluorouracil (5-FU), leucovorin, irinotecan, oxaliplatin] has been extrapolated from the treatment of pancreatic cancer in the metastatic setting. In the ACCORD-11 trial, FOLFIRINOX was found to have a superior survival advantage over gemcitabine in metastatic pancreatic patients with median overall survival of 11.1 months vs. 6.8 months [25]. This study ultimately launched FOLFIRINOX into new treatment paradigms in the adjuvant and neoadjuvant settings.

The phase III PRODIGE 24/CCTG PA.6 trial compared a modified FOLFIRINOX regimen against single-agent gemcitabine therapy, as the results of the ESPAC-4 were not known at study design. This study used a modified FOLFIRINOX regimen: oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and irinotecan 180 mg/m^2 (dose reduced to 150 mg/m^2 after patient 162) on day 1 and continuous fluorouracil infusion 2.4 gm/m^2 over 46 hours. This regimen was repeated every 2 weeks for 12 cycles. The gemcitabine regimen was 1000 mg/m^2 once per 3 of 4 weeks for 6 cycles [26]. The response rate was 31.18% in the mFOLFIRINOX group and 11.3% in the gemcitabine group. The disease-free survival (DFS) and overall survival (OS) in the mFOLFIRINOX arm were 21.6 and 54.4 months, while the gemcitabine arm were 17.7 and 35.0 months repetitively. Grade 3 or 4 adverse events (neutropenia, diarrhea, neuropathy) were significantly higher in the FOLFIRINOX treatment arm than the gemcitabine arm [26].

mFOLFIRINOX has been the largest advancement in overall survival for resected pancreatic cancer patients, which more than doubled the previous median overall survival.

2.4 Radiation therapy

There are mixed opinions regarding the routine use of radiation therapy in pancreatic cancer. The ESPAC-1 did not reveal any significant survival benefit with chemoradiation [19]. A meta-analysis of five randomized controlled trials using adjuvant chemoradiation in patients who underwent curation resection was performed to assess the survival benefit. It appeared that adjuvant chemoradiation had benefitted the subset of patients with a positive margin status; however, it was not statistically significant [27].

The RTOG study looks to determine if the addition of gemcitabine to adjuvant fluorouracil chemoradiation improved survival as compared with fluorouracil. Patients were given either fluorouracil (continuous infusion 250 mg/m^2 per day) or 30 minutes infusion of gemcitabine (1000 mg/m^2 once a week) for 3 weeks prior to fluorouracil chemoradiation and for 12 weeks following chemoradiation. The median survival for the gemcitabine group was 20.5 months, while the median

survival for the fluorouracil group was 16.9 months. There appeared to be a survival benefit, but it was not statistically significant [28].

The LAP07 randomized clinical trial aimed to assess if chemoradiation would improve overall survival after 4 months of gemcitabine and to assess erlotinib's effect on survival as well as in patients with locally advanced pancreatic cancer. There was no difference in overall survival between the chemotherapy alone vs. the addition of chemoradiation, 16.5 months vs. 15.2 months [29].

While variations may occur at different institutions, a common approach for resectable pancreatic cancer would include the surgical resection of the cancer followed by adjuvant chemotherapy. The use of radiation may be used in the adjuvant setting for positive margins following chemotherapy after proving no metastatic disease developed.

3. Treatment of borderline and locally advanced disease

3.1 Neoadjuvant therapy

For patients that present with borderline resectable and locally advanced pancreatic cancer, neoadjuvant chemotherapy with or without chemoradiation allows for systemic control and may improve the likelihood of a R0 resection. The initial rationale for upfront therapies is to potentially downstage tumors to become resectable with a higher R0 resection rate and to allow potential latent metastatic disease to declare itself. In addition, the use of neoadjuvant chemoradiation may be used to "sterilize" the tumor margins near vessel involvement. This allows for selection of the most appropriate patients who have the highest likelihood of long-term survival.

Based on the ACCORD-11 trial showing superior response to FOLFIRINOX, this regimen has now been used effectively in the neoadjuvant setting for borderline and locally advanced pancreatic cancers. Several series have been published showing institutional success. The Massachusetts General Hospital reported that patients treated with mFOLFIRINOX have significantly smaller tumors and lower rates of lymphovascular invasion and perineural invasion. The R0 resection was 92% [30]. Similar reports from the Ohio State University were also noted. They were also able to convert locally advanced and unresectable pancreatic cancers to resectable in 51% of patients who underwent neoadjuvant mFOLFIRINOX with R0 resection of 86% [31].

While patients are undergoing neoadjuvant chemotherapy, serial imaging with pancreatic protocol CT is used to observe for treatment response. In those patients that develop metastatic disease or progression to unresectable disease while undergoing neoadjuvant, their poor biology of disease had declared itself, and they were spared the major morbidity of a surgical resection. For those demonstrating stable or treatment response, the radiologic imaging can be used to predict treatment response. The appearance of the tumor and pancreatic parenchyma interface that becomes more distinct indicates a cytotoxic response which ultimately translates to pathologic response. The ideal response is for the tumor to pull away from the vessels and no longer see haziness around the vessels, which may indicate an infiltrative process. Another prognostic marker of treatment response is normalization of CA 19–9 during neoadjuvant therapy [32].

A pathologic complete response (pCR) can be found in approximately 10% of patients treated in the neoadjuvant approach with FOLFIRINOX and chemoradiation. This is also an independent prognostic risk factor for improved overall and disease-free survival [33]. Additionally, small tumor size, negative

margins, and negative lymph node metastasis are favorable prognostic indicators for improved overall and disease-free survival.

The consensus for treatment of borderline resectable pancreatic cancer favors the neoadjuvant approach; however, it may vary per institution. After a multidisciplinary review at our hospital, the typical functional patient would undergo neoadjuvant chemotherapy (FOLFIRINOX) for 3–4 cycles followed by restaging with CT and CA 19–9. If stable or responding disease, then the patient would continue additional 3–4 cycles of FOLFIRINOX. The patient would again be restaged with CT and CA 19–9. Barring no metastatic disease developed and there was treatment response, the patient would then undergo surgical intervention. However, if the surgical margins were still threatened and there was concern for R1 resection, then the patient may undergo chemoradiation to "sterilize" the margins. Approximately 4–6 weeks after chemoradiation, the patient would ultimately undergo surgical resection.

4. Unresectable pancreatic cancer

Unresectable pancreatic cancer means that the tumor cannot safely be removed due to vascular involvement or metastatic disease. Patients may undergo aggressive chemotherapy with FOLFIRINOX, and a few may be able to convert to a resectable cancer. It is of utmost importance for early palliative care interventions in these patients. For those with biliary obstruction, the use of endoscopic biliary stents and percutaneous biliary drains may provide relief from the jaundice. If the tumor is found to be unresectable in the operating room, then palliative hepaticojejunostomy may be performed. Gastric outlet obstruction may also be relieved with endoscopically placed luminal stents. Additionally, surgical bypass may be performed in laparoscopic or open fashion with a gastrojejunostomy.

Pain can also become quite debilitating in patients with locally advanced unresectable pancreatic cancer. Celiac plexus neurolysis can be performed at the time of surgical exploration, or it may be performed by endoscopic or percutaneous routes.

Irreversible electroporation (IRE) is a nonthermal ablative modality which relies on high voltage (maximum 3,000 volts) small microsecond pulse lengths. This is a novel option typically used in locally advanced pancreatic adenocarcinoma of the head or neck that is not amendable to resection. Some institutions are now using IRE to assist with the resection of locally advanced tumors, but this is not standard at this time. The procedure may be performed open or percutaneously. Patients will typical undergo several months of neoadjuvant chemotherapy to not miss occult metastatic disease prior to IRE. IRE can improve progression-free survival from 6 to 14 months and overall survival from 23 to 20 months [34].

5. Clinical trials

There are several active clinical trials investigating additional treatment options for pancreatic cancer. Several phase II trials are looking at the use of targeted agents in addition to systemic chemotherapy. One study is evaluating the safety of niraparib, PARP [poly (ADP-ribose) polymerase] inhibitor, in advanced pancreatic cancer patients [35]. Another clinical trial at the Massachusetts General Hospital is using the checkpoint inhibitor, nivolumab, as programed death-1 (PD-1) inhibition in combination with losartan, FOLFIRINOX, stereotactic body radiation therapy (SBRT), and surgery in advanced pancreatic cancer. This is a three-armed study:

Arm 1 with FOLFIRINOX, SBRT, and then surgery; Arm 2 with FOLFIRINOX plus losartan, SBRT plus losartan, and then surgery; and Arm 3 with FOLFIRINOX plus losartan, SBRT plus nivolumab and losartan, and then surgery [36].

Reviewing the past studies on chemoradiation, one must keep in mind these studies were using monotherapy chemotherapy and conventional fractionated radiation therapy. There are now several clinical trials assessing the role of radiation therapy, specifically SBRT in the setting of FOLFIRINOX. SBRT utilizes high doses of ablative radiotherapy in typically 1–5 fractions.

The ALLIANCE A021501 is a randomized controlled trial using modified FOLFIRINOX regimen (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and infusional 5-fluorouracil 2400 mg/m^2 over 2 days for 4 cycles) in borderline resectable pancreatic head adenocarcinomas. Arm 1 is delivering this regimen for 8 cycles, while Arm 2 is receiving 7 cycles followed by SBRT (33–40 Gy in 5 fractions). The patient then undergoes pancreaticoduodenectomy followed 4 cycles of adjuvant-modified FOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, bolus 5-fluorouracil 400 mg/m^2, and infusional 5-fluorouracil 2400 mg/m^2 over 2 days for 4 cycles). The main aim of this study is to assess 18-month overall survival, R0 resection, and event-free survival [37].

Another randomized controlled trial by the Pancreatic Cancer Radiotherapy Study Group (PanCRS) is assessing the progression-free survival between mFOLFIRINOX alone vs. mFOLFIRINOX and SBRT in locally advanced unresectable pancreatic cancer [38].

Also, a novel class of drug, cancer stemness inhibitors, is being investigated as a potential new treatment for pancreatic cancer. Napabucasin is an oral small molecule that blocks stem cell activity by targeting the signal transducer and activator of transcription 3 pathway. This pathway is believed to be an important pathway in the propagation of stem-cell-mediated cancer cells [39].

6. Conclusion

While pancreatic cancer is still an aggressive malignancy which is often lethal, there have been significant improvements in the systemic chemotherapy which has improved patients' overall survival. In addition, the radiographic quality has improved thus we are better able to appropriately stage patients for resectability from the onset. Future research in the use of targeted and immunotherapy and the promise of SBRT may control to improve the outcomes of pancreatic cancer patients. With the use of multidisciplinary treatment teams, aggressive combination chemotherapies and surgical resections, there is hope for the patients with pancreatic cancer.

Conflict of interest

The authors declare that there are no conflicts of interest.

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