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Chapter 9

Neoadjuvant Treatment for Nonmetastatic Pancreatic Cancer

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Additional information is available at the end of the chapter

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Abstract

Pancreatic adenocarcinoma is one of the most lethal malignancies among solid tumors. Unfortunately, several patients are diagnosed at metastatic stage or with unresectable disease due to vascular compromise involving the pancreas without any chance of curative treatment. There are also two other groups of patients: resectable patients at upfront diagnosis and "borderline resectable" pancreatic cancer patients. This last group represents those patients where surgery is not always possible without a preoperative treatment allowing surgeons to perform an R0 resection. Achieving an R0 resection is the only curative option for pancreatic cancer patients; nevertheless, many R0-resected patients will relapse within 2 years from surgery. Despite adjuvant treatment, reported median overall survival is only 28 months for patients with resectable pancreatic adenocarcinoma; thus, neoadjuvant treatment has been explored in order to improve survival. We aim to describe the controversial reported data and to show the recommendations that are suggested for these patients; however, we need to remark that there is no strong data that support neoadjuvant treatment. Currently, clinical trials are ongoing, and probably soon this approach will become a standard of care among borderline resectable patients and probably in selected resectable patients too.

Keywords: neoadjuvant treatment, pancreas cancer, borderline resectable pancreatic cancer

1. Introduction

Pancreatic cancer is one of the most lethal malignancies among all types of solid tumors. Most of the patients are diagnosed at clinical and radiological late stages when curative

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treatments are no feasible to perform. To date, surgical resection is still the only potential curative treatment for the adenocarcinoma of the pancreas; however, only 15–20% of all the newly diagnosed patients will be candidates for curative pancreatectomy as an upfront treatment.

A complete radiological evaluation defines three subtypes of patients: metastatic and/or unresectable patients, resectable patients, and borderline resectable patients. This last group includes patients with vascular tumor compromise that could become resectable after an adequate neoadjuvant treatment.

The prognosis of the pancreatic cancer is poor, even in those patients with resectable disease who underwent oncological surgery and adjuvant treatments if they were recommended, but also for those patients with borderline resectable disease who achieved oncological resection after neoadjuvant treatment that may include chemotherapy, radiotherapy, or a combination of both. Despite an optimal treatment, many of the resected patients will relapse within the 24 months after completing adjuvant treatment or after surgery. The 5-year survival following pancreaticoduodenectomy is only 25–30% for node-negative and 10% for node-positive tumors. The need to improve these results has led us to the development of new treatment strategies that will be discussed ahead in this chapter.

2. Epidemiology of the adenocarcinoma of the pancreas

As mentioned earlier, pancreatic adenocarcinoma is one of the malignancies with worse prognosis among all solid tumors, with a small number of patients who will achieve cure after an optimal treatment, only if they have access to a good quality of cancer therapies based on specialized oncological surgeons who usually perform pancreas cancer surgery. In the United States, pancreatic cancer is the second most common malignant tumor of the gastrointestinal tract and the fourth malignancy related to cancer death in adults [1], with an estimated incidence of 48,960 new cases by 2015 and 40,560 deaths during the same year. Reported incidence and mortality are slightly higher in men than in women [2]. According to the reports of "Surveillance, Epidemiology and End Results Program" (SEER), the incidence of pancreatic adenocarcinoma is greater in males than in females (male-to-female ratio 1.3:1) and in Afro American population than in white population (14.8 per 100,000 in Afro American males compared with 8.8 per 100,000 in the general population) [3]. Worldwide, pancreatic cancer is the eighth leading cause of death related to cancer in men (138,100 deaths per year) and the ninth cause of death related to cancer among female population (per year) [4].

In some developing Latin American countries, for reasons associated with industrialization and with the increasing life expectancy, pancreatic cancer and biliary tract malignancies are becoming more frequent diseases in adult population regardless of the educational and socioeconomical level. As an example, in Chile, one of the most developed countries in South America, with an estimated population of almost 17 million inhabitants, the reported annual

mortality rate for pancreatic adenocarcinoma was 5.8 for 100,000 in men and 5.6 for 100,000 in women by 2012. Curiously, due to problems with the cancer registries in Chile as in other countries of the region, the reported mortality may be higher than the reported incidence for this malignancy during the same period [5]. Despite the lack of better cancer registries, it is well known that the incidence and mortality rates are similar among patients with pancreatic cancer, and both curves get closer in low- and middle-income countries; nevertheless, in developed countries, the chance of surviving a pancreatic cancer is still low and the incidence rate is just a little higher than the mortality rate.

Assuming a correct diagnosis and a complete staging, there are different rates of mortality among pancreatic cancer patients according to the extension and probability of resection of the whole tumor. The 5-year survival for all the patients is 7.2%. The highest survival is found in 27.1% with very localized disease, but this rate dramatically decreases up to 10.7% for regional disease, and for metastatic disease, the 5-year survival is almost anecdotic with less than 2.5% of survival patients in that space of time [3].

3. Molecular biology and genetics

Several attempts looking for driver mutations and for trying to find target therapies to control pancreatic cancer spread have been made. Unfortunately, despite all the efforts, researchers have not conducted positive results in the clinical field, or at least their impact has not been relevant. Driver mutations such as KRAS, CDKN2A, TP53, and SMAD 4 have been involved in pancreatic cancer tumorigenesis [6], but without any impact on patients' selection of treatment yet. In other side, current immunotherapies that have achieved a great impact in the treatment of malignancies such as melanoma, lung cancer, bladder cancer, and others were not able to show benefit when tested in pancreatic cancer patients [7].

It is estimated that only 4–16% of pancreatic adenocarcinoma has a family history of this disease [8], while the rest of the cases may be considered as sporadic. To have a first-degree relative with an apparently sporadic pancreatic cancer has a moderate effect on the risk to develop this disease (odds ratio (OR), 1.76; 95% confidence interval (CI), 1.19–2.61) [9]. Selective mutations that have a recognized role in ovarian and breast cancer such as BRCA2 and, in a lesser degree, BRCA1 have been associated with familial pancreas cancer [10]. As previously mentioned, there are other selected genes that may have been associated with pancreatic cancer, for example, PALB2 [11], CDKN2A [12], and SMAD4 [13]. There are also genetic syndromes linked to pancreas cancer (e.g., hereditary pancreatitis, HNPCC, familial breast cancer with BRCA2 mutations, p16 mutations, Peutz-Jeghers syndrome, ataxia telangiectasia) [14]. Routine genetic testing for patients with newly diagnosed pancreatic cancer is controversial but it could give some clinical benefit by reducing the risk of associated cancers and by identifying family members of the index case who might benefit from screening for the cancer-predisposing mutation. Nevertheless, this is not considered a standard practice by current guidelines [15].

4. Resectability

For patients with tumors that appear resectable during the baseline staging, based on tomography of the abdomen with pancreatic phase, which together represent probably only the 20% of all pancreatic cancers, surgery remains the only potentially curative treatment option [16, 17]. The conventional surgical procedure for pancreatic cancer of the head and or the uncinate process is the pancreaticoduodenectomy. Conventional pancreaticoduodenectomy (i.e., Whipple procedure) involves removal of the pancreatic head, duodenum, the first 15 cm of the jejunum, common bile duct, gallbladder, and a partial gastrectomy [18]. Many times, despite a good quality of the surgery and adequate adjuvant treatments, pancreatic cancer has recurrences that will not be able to be treated with a curative intention. Complete R0 resections have a high incidence of recurrence before 2 years after surgery [17], R1 and R2 resections will have a higher and faster incidence of recurrence and in general should not be considered as patients who underwent a curative surgery. Among patients who underwent an R0 surgery, 75% of them will have a recurrence due to microscopic metastatic disease that was undetectable at diagnosis, or due to resistance of locoregional residual tumor cells to adjuvant treatments that include adjuvant chemotherapy, adjuvant radiotherapy, or chemoradiation. Most of the patients who did not achieve a complete resection will relapse with a recurrence rate very close to 100% [19, 20].

At the time of taking decisions to define resectability of pancreatic tumors, a multidisciplinary approach, including surgeons who have expertise in pancreatic tumor resection, medical oncologists, radio- oncologists, and well-qualified radiologists should be mandatory. With the support of specialized radiologists and the rest of the team as well, surgeons will be able to define if the patients may undergo a surgery as an upfront treatment or if they are definitely unresectable (including locally advanced unresectable disease and metastatic disease).

A third group will be considered as "borderline" resectable patients. "Borderline resectable" definition is variable and somehow imprecise. As a global conception of this definition, we might consider that borderline pancreatic cancer involves those patients who, based on images and on oncological surgery team expertise, are not considered as unresectable but at the same time are not clearly resectable as an upfront treatment but could became resectable after a neoadjuvant treatment.

Some reserve the term "borderline resectable" for cases where there is focal (less than one-half of the circumference) tumor abutment of the visceral arteries or short-segment occlusion of the superior mesenteric vein or portal vein confluence. Others suggest that venous narrowing without occlusion should be included in the definition of borderline resectable disease [21]. Due to that, the aim of surgery in pancreatic cancer is to achieve an RO resection to give the chance of a curative treatment; borderline resectable patients are the best candidates to be treated with neoadjuvant therapies, and most of the time they should not undergo surgery as a first treatment due to a higher risk of not achieving a complete resection resulting in a potential negative impact in survival.

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5. Adjuvant therapy in pancreatic adenocarcinoma

Until recently, gemcitabine chemotherapy was the standard of care as adjuvant treatment in complete resected pancreatic cancer patients [22]. The use of radiation therapy or chemoradiation has been controversial, without clear data to support its use among complete resected patients [23, 24]; however, there are groups that considered its use [25] mainly in the group of R1-resected patients and or among node-positive patients. It is important to remark that most of the recurrences will be distant metastasis and only a small percentage of patients will die due to local recurrence or due to local progression after resection; therefore, systemic treatments should always be considered unless a clear justification for local regional treatment has been made.

Since 2017, the standard of care for early stage, resectable pancreatic adenocarcinoma patients is surgery followed by adjuvant chemotherapy combination of gemcitabine plus capecitabine according to ESPAC-4 trial. The median overall survival for these patients in the gemcitabine plus capecitabine group was 28.0 months (95% CI, 23.5–31.5) compared with 25.5 months (22.7–27.9) in the gemcitabine group (hazard ratio (HR) 0.82 (95% CI, 0.68–0.98), p = 0.032). Reported results showed a positive impact for the adjuvant therapy in most of the clinical subgroups, including patients with R1 resection margins [26].

S-1 is an oral 5 FU prodrug that has been tested in several malignancies with good results but with a limited efficacy among Asian population. In the phase III JASPAC 01 trial, adjuvant chemotherapy with S-1 showed a 5-year overall survival rate of 43.6 versus 24.2% for gemcitabine (HR 0.60; P < 0.0001) and was relatively well tolerated [27]. These data support the use of S-1 as a new standard of care for adjuvant treatment among Japanese population that underwent surgery for pancreatic adenocarcinoma, but it should not be considered in non-Asiatic population due to the lack of existing data.

The use of adjuvant chemotherapy can be delayed or affected by postoperative complications but also by the appearance of early recurrences that can be found before systemic treatment starts or during early image control during adjuvant treatment. Prospective observational trials have shown that up to 38% of resected pancreatic cancer patients did not receive chemotherapy due to those reasons [28, 29]. Considering the bad prognosis of this disease, despite a complete resection when feasible, neoadjuvant treatments have been explored, which focused on improving those outcomes.

6. Locally advanced and unresectable disease

Locally advanced unresectable and metastatic pancreatic cancer patients have a similar dismal prognosis. In case of patients with a good performance status (ECOG 0–1), they should be strongly considered for treatment with high-intensity palliative chemotherapy, with the aim of improving quality of life and overall survival. Conroy et al. showed in the PRODIGE trial that FOLFIRINOX regimen when compared with gemcitabine was associated with a significative

better survival, with a reported median overall survival of 11.1 months versus 6.8 months, respectively (HR for death 0.57 (95% CI, 0.45–0.73), p < 0.001) [30]. This trial was basically conducted among French population and did not include patients of 76 years or older. In patients with ECOG 2 and those with ECOG 0–2 older than 75 years, a lower intensity chemotherapy regimen like gemcitabine with or without nab-paclitaxel should be considered. Von Hoff et al. published in 2013 that the combination of gemcitabine and nab-paclitaxel improves overall survival compared with gemcitabine alone (median OS 8.5 vs. 6.7 months, HR 0.72, CI 0.62–0.83, P < 0.001) [31]. Patients older than 75 years were also included in this study. Chemotherapy should not be recommended in patients with a poor performance status (ECOG 3–4) due to lack of benefit and because a higher risk of toxicity with worsening of quality of life.

7. Neoadjuvant treatment

Regardless of the relative poor prognosis of the disease and considering that an adequate treatment is the only option for surviving a pancreatic cancer, resectable and borderline resectable pancreatic cancer patients should be considered for curative intention treatments [32].

Theoretically, treating patients with neoadjuvant chemotherapy might favor the eradication of microscopic metastatic disease to obtain better results in terms of survival. It may also help in making a "selection" of patients to undergo surgery: if the patient presents disease progression during treatment, an unnecessary surgery could be avoided in patients that otherwise would have had a rapid disease progression after surgery, considering also that oncological surgery for pancreatic cancer is not free of morbidity and mortality [33].

A decision analysis model to assess what was the best treatment strategy for resectable pancreatic cancer supported the use of neoadjuvant chemotherapy showing that it provided longer survival in comparison to surgery followed by adjuvant chemotherapy [34].

Geus et al. [35] reviewed 12,857 non-metastatic pancreatic adenocarcinoma patients who underwent pancreatectomy and initiated adjuvant chemotherapy. Across propensity score-matched analysis, comparing the clinical outcomes of neoadjuvant therapy versus upfront surgery for pancreatic cancer by stage, neoadjuvant therapy was associated with a significant survival benefit after matching (median survival 22.9 vs. 17.3 months; log-rank P < 0.0001) compared with conventional upfront surgery followed by adjuvant therapy, in stage III patients.

Mokdad et al. [36] reviewed the data from a cohort of 15,237 patients (National Cancer Database 2006–2012) with stage I–II adenocarcinoma of the head of the pancreas that were treated with curative intention, comparing neoadjuvant treatment (chemotherapy or chemoradiotherapy combination) with patients who underwent upfront resection with or without adjuvant treatments (chemotherapy or chemoradiotherapy combination) to evaluate the overall survival impact of those modalities. The authors of this manuscript showed that patients who had received neoadjuvant treatment had better results in terms of survival when compared with patients who underwent surgery as an upfront treatment. The median survival

was 26 months for the neoadjuvant group and 21 months for the group who underwent surgery as an upfront treatment, but also a higher pathological tumor stage, a higher incidence of lymph node compromise, and a lesser R0 resection in the group that did not receive neoadjuvant treatment were seen. A two-arms Markov model showed that the median overall survival was longer for the neoadjuvant cohort (22 months) in comparison with the adjuvant group (20 months) [37]. Despite this information that shows better outcomes in terms of survival when neoadjuvant treatments have been done, to date, there are no phase 3 randomized clinical trials that support the use of neoadjuvant treatments in pancreatic cancer patients. Most of the available data are limited to retrospective evidence or to one-arm design-prospective clinical trials [38].

In recent years, the use of systemic preoperative chemotherapy alone or in combination with radiation therapy has been offered to an increasing number of patients with the main intention of reducing the size of the tumor, increasing the likelihood of negative resection margins, and testing the effects of cytotoxic medications in vivo [39].

Phase 2 clinical trials have evaluated the use of neoadjuvant therapy for resectable and borderline resectable pancreatic cancer patients, either with chemotherapy or with chemoradiotherapy combination (**Table 1**).

One quarter of the patients who underwent neoadjuvant chemoradiotherapy had disease progression, and surgery was not performed. Disparities on reported results among patients who underwent surgery showed an R0 resection rate between 12.5 and 96% of the total resected patients. Patients who had progression after treatment did it mainly with distance metastasis (59–73%), most of them located at the liver. Local recurrence rate was seen between 0 and 25% according to different reports. Reported overall survivals show also differences; patients who only received neoadjuvant treatment with chemoradiation had reported survival between 8 and 34 months; patients who underwent only neoadjuvant chemotherapy achieved survivals up to 19 months.

Chemotherapy without radiation has been explored as an option for neoadjuvant treatment in pancreatic cancer. A phase 2 clinical trial in the neoadjuvant setting using gemcitabine with or without cisplatin showed a resection rate of 54% and a median overall survival of 28 months in resected patients [40]. Unfortunately, similar trials using gemcitabine plus cisplatin doublet showed inferior results [41]. Due to the heterogeneity of these studies that included different types of patients such as resectable, borderline resectable, and unresectable patients at diagnosis, but also that have used different modalities of radiotherapy and different schedules and schemes of chemotherapy, no conclusion can be drawn regarding the overall impact on survival and what are the most effective chemotherapy agents or the best combination of chemotherapy agents for resectable pancreatic cancer.

Since 2011, after the results of PRODIGE trial, many case series with neoadjuvant FOLFIRINOX for locally advanced pancreatic cancer have been published, but sample sizes of most studies have been too small to draw definitive conclusions about the efficacy and safety of this treatment approach; however, its use followed by chemoradiation as a multimodality treatment has shown promising results (**Table 2**).

Author / Year	No. Patients	Clinical Stage / Duration Noad. therapy	Chemotherapy / Radiation	Radiological Response (%)	R0 resection (%)	Median Overall survival (mo)
Jessup/ 1993	16	Unresectable / NA	Fluorouracil (IC 225 mg/m2) 7 days per week / 45Gy	Partial: 20 Progression: 62	12.5	8 protocol vs 12.2 nonprotocol
Hoffman/ 1998	53	Resectables / 2.8 mo	Mitomycin 10 mg/m2 day 2 and fluorouracil 1,000 mg/m2/d continuous infusion / 50 Gy	Partial: 8 Progression: 16	67	15 surgery with resection vs 8.3 surgery witout resectoin
Talamonti/ 2006	20	Resectables / 3.8 mo	Gemcitabine (1000 mg/m2 weekly) / 36Gy	Partial: 15 Progression: 5	94	26 with surgery vs NA
Palmer/ 2007	26	Resectables / 4 mo	Gemcitabine (1000 mg/m2 weekly) + Cisplatin (25 mg/m2)	Partial: 0 Progression:4	75	28.4 with surgery vs 8.6 Bypass
Le Scodan/ 2009	41	Resectable / 3 mo	5-FU (300 mg/m2 daily) + Cisplatin (20 mg/m2) / RT (50 Gy)	Partial: 10 Progression 25	81	11.7 with surgery vs 5.7 nonoperated
Heinrich/ 2008	28	Resectable / 2mo	Gemcitabine (1000 mg/m2 twice weekly) + Cisplatin (50 mg/m2)	Partial: 4 Progression: 13	80	19.1 with surgery
Evans/ 2008	80	Resectable / 3 mo	Gemcitabine (400 mg/m2 weekly) / 30 Gy	NA	82	34 with surgery vs 7 without
Varadhachary/ 2008	90	Resectable / 4.3 mo	Gemcitabine (750 mg/m2 weekly) + Cisplatin (30 mg/m2) every 2 wk / 30Gy	NA	96	31 with surgery vs 10.5 without
Landry/ 2010	21	Resectable / 3 mo	Arm A: Gemcitabine (500 mg/m2) weekly + RT (50 Gy) Arm B: Gemcitabine (175 mg/m2) + Cisplatin (20 mg/m2) + 5-FU (600 mg/m2) +RT (50 Gy)	Arm A Partial: 10, Progression: 10, Arm B Partial: 18, Progression: 36	NA	26.3 with surgery vs NA
O´Reilly/ 2014	38	Resectable / 2mo	Gemcitabine (1000 mg/m2) + Oxaliplatin (80 mg/m) every 2 wk for 4 cycles	Partial: 10.5 Progression: 7.9	74	27.2 with surgery vs range range of 5 to 32 for unresected
Golcher/ 2015	33	Resectable / 1 mo	Arm B 300 mg/m2 gemcitabine and 30 mg/m2 cisplatin on days 1, 8, 22, and 29 of radiotherapy / 50Gy	NA	Arm B: 48	25 Arm B vs 18.9 Arm A (surgery First)
Van Buren/ 2013	59	Resectable / 2 mo	Gemcitabine (1500 mg/m2) ever 2 wk + Bevacizumab (10 mg/kg) + RT (30 Gy)	Partial: 8.4 Progression: 7.9	88	19.7 with surgery vs NA

Noad: Neoadyuvant, IC: Infuses continuous, NA: Not Available, Mo: Month

Table 1. Phase II trials of patients treated with neoadjuvant therapies.

In general, according to data mainly obtained from retrospective studies with a small number of patients with disease in borderline and locally advanced stages, between 13 and 68% of patients could undergo surgery after neoadjuvant treatment, achieving R0 resection in a range of 24–100%, with a median survival that usually exceeds 20 months.

Published results of a meta-analysis that included 13 different publications, with different methodologies including 325 patients with locally advanced pancreatic cancer treated with FOLFORINOX regimen, with some of the patients that after this treatment underwent radiotherapy or chemoradiation, showed that 28% of the patients (91 of 325 included in this analysis) underwent surgery with a pooled proportion of patients who achieved R0 surgery of 78% [42]. In this same meta-analysis, which included a total of 689 patients with different stages, as mentioned before, all received FOLFIRINOX; some of them underwent other therapies such as radiation or radio-chemotherapy, and not all the patients treated with FOLFIRINOX as neoadjuvant treatment could undergo surgery, the reported median overall survival across all the studies was 10–32.7 months and the reported progression-free survival ranged from 3 to 20.4 months.

In a small multicenter prospective single-arm trial that included 22 borderline resectable pancreatic cancer patients, Katz et al. assessed the use of four cycles of neoadjuvant-modified

Author/year/type	No. patients with Noady FOLFIRINOX/ total	Clinical stage	Radiation	Resection	R0 resection (%)	Median overall survival range (mo)
Boone/2013/ Retrospective	25/ 25	BR: 12 (48%), LA: 13 (52%)	SBRT 36 Gy	11 (44%)	7 (63%)	NA
Faris/2013/ Retrospective	22/ 22	LA: 22 (100%)	IMRT 50.4 Gy	12 (54.5%)	5 (42)	24.7 (19.0–30.3)
Ferrone/2015/ Retrospective	40/127	BR:15 (12%), LA 25(20%)	CHRT: 50.4 Gy and 5-FU*	40 (31.4%)	35(92)	34
Hosein/2012/ Retrospective	18/18	BR 4 (22%), LA 14 (78%)	CHRT: 50.4 Gy and GEM**	10 (55.5%)	8 (80%)	32.7 (23.1-42.3)
Marthey/2015/Cohort	77/77	LA: 77 (100%)	54 Gy***	28 (36.3%)	25 (89)	22 (12.3-29.9)
Mellon/2015/ Retrospective	21/159	BR 110 {69%), A: 49 (31%)	SBRT 30-40 Gy#	21 (13.2%)	5 (24)	15
Sadot/2015/ Retrospective	101/101	BR: 31 (30.6%), LA: 70 (69.3%)	CHRT¨	31 (30.6%)	16 (52)	26 (18-33)
Katz/2016/ Prospective single-arm	22/22^	BR 22 (100%)	CHRT 50.4 Gy^	15 (68%)	15 (100)	21.7

Noady: neoadjuvant, BR: borderline resectable, LA: locally advanced, SBRT: stereotactic body radiosurgery, IMRT: intensity-modulated radiation therapy, HIGRT: hipofractionated radiation therapy, NC: not correspond, CHRT: chemoradiation, 5-FU: fluorouracil, GEM: gemcitabine.*After FOLFIRINOX and before surgical exploration.

**For unresectable patients post FOLFIRINOX, radiation sensitization patients received concurrent gemcitabine plus IMRT.

***External radiotherapy for consolidation.

#After neoadjuvant chemotherapy.

¨Patients who appeared to convert to resectable disease underwent surgical exploration, and patients with stable disease were typically initiated with chemoradiotherapy with 5-FU or GEM.

^Modified FOLFIRINOX treatment: (85 mg/m^2 of oxaliplatin, 180 mg/m^2 of irinotecan hydrochloride, 400 mg/m^2 of leucovorin calcium, and then 2400 mg/m^2 of 5-fluorouracil for 4 cycles) followed by 5.5 weeks of external-beam radiation (50.4 Gy delivered in 28 daily fractions) with capecitabine (825 mg/m^2 orally twice daily) prior to pancreatectomy. 10 patient initiated adjuvant therapy with GEM.

Table 2. FOLFIRINOX studies only with BR and LA pancreatic cancer.

FOLFIRINOX followed by 5.5 weeks of radiation therapy with a total dose of 50.4 Gy in 28 fractions with concurrent capecitabine twice daily during radiation [43]. Grade 3 or higher toxicity was reported in 64% of patients. Fifteen patients underwent pancreatectomy, 80% of them required vascular resection, and R0 resection was achieved in 93% of the resected patients. The reached median overall survival was 21.7 months. Using another regimen of neoadjuvant chemotherapy, a single patient case report showed efficacy achieving R0 resection in this patient who had unresectable locally advanced diseased and was treated with gemcitabine plus nab paclitaxel combination followed by FOLFIRINOX before surgery [44].

To address the question if neoadjuvant treatments or adjuvant treatments will result with better outcomes, different prospective trials are currently ongoing, and their aim is to find out the real impact of the neoadjuvant treatments in resectable and borderline resectable pancreatic cancer patients. Those trials include neoadjuvant chemotherapy, neoadjuvant versus

adjuvant chemotherapy, neoadjuvant chemoradiation, neoadjuvant chemoradiation versus upfront surgery, and other modalities as well [45–49].

Concerning toxicity among patients treated with neoadjuvant treatments that have been reported, mostly as local experiences or as small institutional trials, there are no clear data concerning side effects of neoadjuvant therapies, nor there are data on perioperative morbidity and mortality, comparing patients who underwent upfront surgery and patients who received neoadjuvant treatment and then underwent surgery. The biggest data on quality of life come from reports in the metastatic setting. The quality of life report of the PRODIGE-4 trial (mentioned earlier), FOLFIRINOX chemotherapy reduced the quality of life impairment compared with gemcitabine, but also it has benefit in the quality of life that can be a surrogate for survival, as physical functioning and some symptoms severity were prognostic factors for survival [50]. In a meta-analysis of FOLFIRINOX in locally advanced pancreatic cancer, 60% of the patients presented G3 or higher side effects, neutropenia and diarrhea being the most frequent events among treated patients. There were no related deaths attributable to FOLFIRINOX [42]. In a retrospective analysis of patients undergoing FOLFIRINOX as neoadjuvant treatment followed by surgery, Marchegiani et al. concluded that among patients who underwent neoadjuvant chemotherapy, there were less postoperative pancreatic fistula and less postoperative pancreatic hemorrhage but delayed in gastric emptying [51].

8. Current guidelines

Due to a lack of strong data based on phase 3 clinical trials, it is not possible to talk about a gold-standard treatment in the neoadjuvant setting for pancreatic cancer patients. Most of the groups support the idea to perform surgery as an upfront treatment in resectable patients followed by adjuvant chemotherapy.

Current ESMO guidelines support the use of FOLFIRINOX followed by chemoradiotherapy in borderline resectable patients as a main option in pancreas cancer [52]. Contrarily, ASCO guidelines indicate that there is no clear evidence to support one regimen over another, and physicians may offer therapy based on extrapolation from data derived from studies in the metastatic setting [53].

Pancreatic cancer patients with resectable or borderline resectable disease should always be discussed in a multidisciplinary team. Neoadjuvant treatment should always be considered to attempt an R0 resection; otherwise, the chance of cure in non-R0-resected patients and also due to the meaning of the diagnosis itself will be similar to metastatic patients. Multidisciplinary team should at least include a digestive oncological surgeon with expertise in pancreatic surgery, a medical oncologist, a radiologist with expertise in pancreas, a radiation oncologist, and a pathologist, given the disparity of opinions and the importance of treatment agreement looking forward the best chance to those patients.

At SLAGO 2015 (Latin American Gastro-Enterology Cancer Symposium) congress [54], a meeting held every 2 years in Latin America that focuses on digestive malignancies, specialists from different Latin American countries met to discuss about pancreatic cancer. Concerning

borderline resectable pancreatic cancer patients, SLAGO's main recommendation is to consider FOLFIRINOX schedule as the best choice for neoadjuvant treatment; then after selected patients that do not have disease progression after chemotherapy could be considered for radiotherapy with capecitabine as radio-sensibilizer before surgery. For patients who have contraindication to receive FOLFIRINOX and in older than 76 years, neoadjuvant treatment with gemcitabine plus nab paclitaxel combination can be an option [55].

9. Conclusions

Pancreatic cancer is one of the most lethal malignancies among all types of solid tumors. Most of the patients are diagnosed at unresectable or at advanced stages with no chances of cure. Early diagnosis is critical to give the patient the chance of cure; however, most of the patients are diagnosed where the tumor is not amenable to be resected. Even more, many of the patients who will undergo an R0 resection will relapse before 2 years after surgery.

We would like to remark that there is no strong evidence to make final conclusions in order to define the best upfront treatment in non-metastatic resectable and borderline resectable pancreatic cancer patients. For resectable patients at diagnosis, upfront surgery is still the standard of care followed by adjuvant chemotherapy. In this subgroup of patients, radiotherapy and chemoradiotherapy do not seem to be the best choice. On the other hand, neoadjuvant chemotherapy has not been explored yet in well-designed clinical trials, and its use has been just limited to small experiences. Borderline resectable pancreatic cancer patients are a subgroup where upfront surgery has a low chance of achieving an R0 resection; therefore, these patients must be considered to receive neoadjuvant treatments in order to improve complete tumor resection and as a consequence to improve survival. As in the resectable subset of patients, radiotherapy or chemoradiotherapy has not shown a real impact in this group. FOLFIRINOX followed or not by chemoradiotherapy seems to be the best option to improve resectability, for achieving complete resection and pathological downstaging and for improving overall survival in resected patients. Final reports from clinical trials will set the key whether or not neoadjuvant treatment, in resectable and borderline resectable pancreatic cancer patients, should be mandatory or recommended.

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