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Pancreatic Cancer in the Era of Neoadjuvant Therapy: A Narrative Overview

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Rezumat

Cancerul de pancreas în era tratamentului neoadjuvant: prezentare generală

Adenocarcinomul pancreatic este o boală sistemică agresivă, aproximativ 30% din pacienți prezentând la diagnosticare un stadiu local-avansat nerezecabil. Pionieratul tratamentului neoadjuvant pentru cancerul pancreatic local-avansat (LAPC) a început acum mai bine de 25 de ani ajungând să fie folosit tot mai mult. În ultimii ani s-au realizat două lucruri importante: în primul rând, au fost publicate definiții clare ale tumorilor rezecabile, borderline şi ale tumorilor local-avansate nerezecabile, iar în scurt timp au fost introduse două scheme terapeutice de chimioterapie (FOLFIRINOX şi Gemcitabină plus Nab-Paclitaxel) după ce a fost demonstrată eficiența lor în practica clinică pentru pacienții cu LAPC şi metastaze. Acest articol analizează articole publicate în perioada 2011 - 2017, privind administrarea chimioterapiei neoadjuvante, însoțită sau nu de radioterapie, subliniind mai ales rezultatele raportate în ceea ce priveşte ratele de rezecție, ratele complete de rezecție (R0) şi rata de supraviețuire globală, rezumând recomandările furnizate de cele mai recente ghiduri pentru tratamentul cancerului pancreatic nemetastatic.

Cuvinte cheie: adenocarcinom pancreatic, cancerul pancreatic local-avansat, terapie neoadjuvantă, FOLFIRINOX, Gemcitabină, prognostic

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Abstract

Pancreatic adenocarcinoma is an aggressive systemic disease with

around 30% of patient presenting locally advanced disease at diagnosis and being not candidate to surgical resection. Pioneering experiences with neoadjuvant treatment for locally advanced pancreatic cancer (LAPC) were undertaken more than 25 years ago and this strategy kept on gaining consensus over time. In recent years two main breakthroughs have been done: first, clear definitions of resectable, borderline resectable and locally advanced unresectable disease were released, and, soon after, two different chemotherapy regimens (namely, FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel) were introduced in the clinical practice for LAPC after their effectiveness in metastatic patients was demonstrated. This article reviews papers regarding the administration of neoadjuvant chemotherapy, with or without radiation therapy, published from 2011 through 2017 with particular significance been given to reported results in term of resection rates, complete resection (R0) rates and Overall Survival, and briefly summarizes recommendations provided by the most recent guidelines for the treatment of non-metastatic pancreatic cancer.

Key words: pancreatic adenocarcinoma, locally advanced pancreatic cancer, neoadjuvant therapy, FOLFIRINOX, Gemcitabine, prognosis

Introduction

Pancreatic adenocarcinoma is an aggressive systemic disease with increasing incidence and poor prognosis, with around the 8% of patients being alive after 5 years since diagnosis when considering all stages (1). The survival rates have been substantially unchanged during the last decades (2). The majority of patients are diagnosed with metastatic disease, and are treated with first-line chemotherapy, whenever possible. Conversely, for patients presenting with a radiologically resectable disease (counting for around 20%) the standard of care is represented by a radical resection possibly followed by adjuvant chemotherapy with or without radiation therapy. This strategy can provide a median survival exceeding 2 years (3). In the latest years, much effort has been spent for improving outcomes in patients with locally advanced, unresectable disease at diagnosis, In this set of patients, neoadjuvant therapy with newly introduced regimens has been introduced in clinical practice in the attempt to increase resectability. The present review focuses on the multimodal treatment of non-metastatic pancreatic ductal adenocarcinoma (PDAC), and discusses the most recent advances in the field of neoadjuvant systemic therapy.

Background

Non-metastatic PDAC is anatomically defined as resectable (R), borderline resectable (BR), and locally advanced (LA) on the basis of venous and arterial involvement on cross-sectional imaging. In general, vascular involvement has been shown to be associated with higher rates of microscopically incomplete resection, longer operative time and higher perioperative morbidity (4,5). Different criteria defining resectability status have been proposed, including the AHPBA/SSAT/SSO/GSSC expert consensus guidelines (6), the NCCN guidelines (7), and the International Study Group of Pancreatic Surgery (ISGPS) guidelines (8). Because these criteria are based on cross-sectional imaging features, high-quality radiologic staging is mandatory. Dedicated pancreatic-protocol CT study and MRI study are nowadays equally sensitive in staging (9) but CT scan remains the most common choice.

In patients with BR and LA PDAC, neoadjuvant chemotherapy, with or without radiation therapy has been employed commonly. The rationale for its use is well established: first, to obtain a down-sizing and possibly a down-staging of the tumor in order to increase

the likelihood of complete resection. In fact R status and N status are considered the most relevant determinants for prognosis in patients undergone surgery, together with tumor dimension (10-14). The administration of preoperative chemo or chemo-radiation may be a useful strategy to deliver patients the maximum load of chemotherapy (15), since 40% of patients will never qualify for adjuvant treatments due to the high morbidity rate of pancreatic resections or poor performance status (16). Another theoretical advantage of initial systemic therapy is the chance to treat occult micrometastases since the time of diagnosis, trusting to hit those cancer foci responsible of rapid recurrence following resection (17) and select those patients who really could benefit from surgery. Furthermore, delivering chemotherapy drugs before surgery should let them fully penetrate cancer cells since pancreatic tissue is still not altered by inflammation and fibrosis which are consequences of the surgical procedure.

Preoperative treatment has been demonstrated to be effective in different gastrointestinal malignancies (18-20). The first clinical experiences in pancreatic cancer showed the utility of these approach more than 25 years ago (21,22); since then the use of preoperative combined therapies has rapidly increased.

According to a large meta-analysis published by Gillen et al. in 2010, 47% of patients deemed unresectable at diagnosis was surgically explored after neoadjuvant therapy delivery, and resection was successfully completed in 70% of them with a R0 rate of 82% (23). The highest resection rate was obtained using combination chemotherapy instead of monotherapy (33%, CI 25.2%-41.3% vs 27.3% CI 18.1%-37.5%). Progressive disease was diagnosed in 20.8% during treatment and grade 3 and 4 toxicity occurred in 29.4%. Considering the whole amount of patients in the 111 trials reviewed (namely, 3494 patients diagnosed with either resectable cancer and BRPC) the estimated postoperative morbidity and in-hospital mortality were 34.2% and 5.3% respectively, comparable to those of patient undergone upfront surgery. Finally, when resection was achieved median survival was 23.3 months for resectable patients before treatment and 20.5 months for LAPC patients: for the former group no improvement was found compared to upfront surgery followed by adjuvant chemotherapy, but for the latter the advantage was clinically relevant, considering that life expectancy was similar to that of initially resectable tumor patients. However, this review included papers published since 1980 through December 2009. Different combinations of agents and dosages were adopted, with the most common used being gemcitabine, 5-FU and its analogues, mitomycin C and platinum compounds. Furthermore, in 93% of studies radiation therapy was administered before surgery with different schedules.

A meta-analysis by Dhir et al. (24) including 96 series published from 2009 through 2015 reported resection rates of 76%, 69% and 26% for resectable, BRPC and LAPC respectively after neoadjuvant therapy, with R0 rates ranging from 63% among resectable to 23% among unresectable patients. On average 59% of patients showed stable disease at re-staging. Complete response was very rare (<1%). Disease progression was quite uncommon (16% of patients) with the higher rate accounting for 21% in the primarily unresectable subgroup. This data overlapped to that one detected by Gillen and colleagues in their earlier study (23). Not surprisingly the longer overall survival was seen for patients with resectable disease (30 months); for BRPC and LAPC patients estimated overall survival were 27.4 and 18.7 months respectively.

This paper confirmed the good results obtained with neoadjuvant protocols in more recent years. Once again, the Authors reported better results in term of prognosis with the administration of multi-agent therapy; the longest overall survival was reached when FOLFIRINOX was administered.

In 2011 and 2013 multi-agent chemotherapy regimens Nab-Paclitaxel plus Gemcitabine and FOLFIRINOX were demonstrated to be more effective to improve Overall Survival and Progression Free Survival in the metastatic setting compared to gemcitabine alone (25, 26). Thus they were introduced in clinical practice

for metastatic patients with good performance status instead of Gemcitabine monotherapy. Soon they started to be offered to patients with locally advanced disease in the absence of a proven convincing alternative.

Methods

PubMed database was searched using the terms 'pancreatic adenocarcinoma' and 'neo-adjuvant' from 2011 through November 2017. Abstracts reporting the use of neoadjuvant chemo- or chemo-radio-therapy for patients with non-metastatic pancreatic cancer scheduled for eventual surgical resection were selected. Retrospective series, prospective trials and randomized clinical trials were considered for full-text consultation. Case reports and trials including less than ten patients were excluded.

Review of the Literature

FOLFIRINOX as neoadjuvant treatment was the most commonly tested regimen in series published in the last 7 years (*Table 1*).

The earliest experiences with FOLFIRINOX presented by Hosein et al. (27) and Tinchon et al. (28) on a very small number of patients diagnosed with BRPC (4 patients) and LAPC (26 patients considering both the studies) showed good response rates at the expense of a mild toxicity. Survival data were not conclusive due to the small study samples. Mahaseth and colleagues (29) explored the efficacy of FOLFIRINOX on 60 patients diagnosed with either BRPC, LAPC and metastatic cancer. They found a radiologically detectable response in 30% of patients and a decrease of Ca19.9 levels >50% from baseline in 57%. Interestingly reduction of Ca19.9 was not associate with

Table 1. Papers presented in chronological order of publication. Res: resection; mOS: median overall survival; Gem: Gemcitabine; Ox: Oxaliplatin; Cape: Capecitabine; adj: adjuvant therapy; CRTx: chemo-radio-therapy; RTx: radiation therapy; US: upfront surgery; n.r.: not reported; n.a.: not available; RCT: randomized clinical trial

Reference	Type of study	N. of patients	Disease	Period of study	Treatment	Res (%)	R0 (%)	mOS
Berriochoa et al. (34)	Retrospective	21	Resectable/BRPC	2011-2014	Gem or 5FU+RTx vs adj CRTx vs definitive CRTx	58	97	n.r.
Itchins et al. (35)	Retrospective	87	BRPC/LAPC	2010-2016	Gem plus Nab-Paclitaxel or Gem or FOLFIRINOX vs US	79	75	29
Shrestha et al. (36)	Retrospective	97	BRPC	2007-2012	FOLFOX/FOLFIRINOX+RTx or Gem-based regimens+RTx or CRTx	44	95	26
Yoo et al. (37)	Phase II	18	BRPC	2013-2014	FOLFIRINOX	67	75	21
Eguchi et al . (38)	Phase II	34	BRPC/LAPC	2007-2013	Gem+RTx vs Gem+S1+RTx	15	80	43
Fiore et al.(39)	Phase II	34	BRPC/LAPC	2012-2015	GemOx+RTx	55	100	38
Ielpo et al. (40)	Retrospective	45	Resectable/BRPC	2007-2016	Gem plus Nab-Paclitaxel+RTx vs US	69	97	31
Kim et al. (41)	Retrospective	40	BRPC	2007-2015	Gem or 5FU or FOLFIRINOX ±CRTx	85	76	n.r.
Busquets et al. (42)	Retrospective	22	BRPC	2010-2014	GemOx + CRTx	50	63	25
Kluger et al. (43)	Retrospective	56	LAPC	2012-2017	Gem-based or FOLFIRINOX+RTx	All	80	18.5
Grose et al. (44)	Retrospective	85	Resectable/ BRPC/LAPC	2012-2015	GemCape or FOLFIRINOX ±CRTx	38	59	37
De Geus et al. (45)	Retrospective	1541	Resectable/ BRPC/LAPC	2004-2012	Different drugs (n.r.) vs US	n.r.	n.r.	26/23. 5/23
Hackert et al. (33)	Retrospective	575	LAPC/metastatic	2001-2015	FOLFIRINOX vs Gem +CRTx vs others	51	33	22
Katz et al. (46)	Phase II	22	BRPC	2013-2014	FOLFIRINOX±CRTx	68	93	22
Mokdad et al. (47)	Retrospective	2005	Resectable	2006-2012	Different drugs (n.r.) vs US	All	83	26
Hammel et al. (48)	RCT phase III	442	LAPC	2008-2011	Gem vs GemErlotinib ±CRTx	4	61	31

Table 1. Continuation

Reference	Type of study	N. of patients	Disease	Period of study	Treatment	Res (%)	R0 (%)	mOS
Christians et al. (49)	Retrospective	69	Resectable	2009-2013	Gem-based or FOLFIRINOX ±CRTx	87	97	45
Mirkin et al. (50)	Retrospective	1736	Resectable/ BRPA/LAPC	2003-2011	Different drugs (n.r.) ±RTx	All	75.5	23
Casadei et al. (51)	RCT phase II	38	Resectable	2003-2009	Gem+RTx vs US	61	40	n.r.
Golcher et al. (52)	RCT phase II	29	Resectable	2003-2009	GemCisplatinum+RTx vs US	65	89.5	25
Sadot et al. (32)	Retrospective	101	LAPC	2010-2013	FOLFIRINOX±CRTx	31	55	n.r.
Ferrone et al. (53)	Retrospective	40	BRPC/LAPC	2011-2014	FOLFIRINOX±RTx	85	92	34
Blazer et al. (54)	Retrospective	43	BRPC/LAPC	2011-2013	FOLFIRINOX±RTx	51	86	n.r.
Addeo et al. (55)	Retrospective	45	BRPC/LAPC	2007-2012	Gem or GemOx or FOLFIRINOX	All	75.5	21
Marthey et al. (31)	Retrospective	77	LAPC	2010-2012	FOLFIRINOX	36	89	25
Mellon et al. (56)	Retrospective	159	BRPC/LAPC	2009-2014	Gem or FOLFIRINOX +RTx	38	97	34
Khushman et al. (57)	Retrospective	51	LAPC	2008-2013	FOLFIRINOX±RTx	22	45	35
Nitsche et al. (58)	Retrospective	15	LAPC	2011-2014	FOLFIRINOX	29	n.r.	n.r.
Nanda et al. (59)	Retrospective	44	BRPC/LAPC	2010-2013	FOLFIRINOX+CRTx	41	83	n.r.
O'Reilly et al. (60)	Phase II	38	Resectable	2007-2011	GemOx	71	74	27
Rose et al. (61)	Retrospective	64	BRPC	2008-2012	GemDocetaxel	48	87	22
Christians et al. (62)	Retrospective	18	BRPC	2010-2012	FOLFIRINOX+CRTx	67	100	22
Paniccia et al. (63)	Retrospective	18	BRPC	2011-2013	FOLFIRINOX+CRTx	89	100	n.r.
Kim et al. (64)	Phase II	68	Resectable/ BRPC/LAPC	2007-2010	GemOx+RTx	63	84	25
Boone et al. (65)	Retrospective	25	BRPC/LAPC	2011-2012	FOLFIRINOX+CRTx	28	33	n.r.
Faris et al. (30)	Retrospective	22	LAPC	2010-2012	FOLFIRINOX+CRTx	23	100	n.r.
Mahaseth et al. (29)	Cohort	60	BRPC/LAPC/ metastatic	2010-2012	FOLFIRINOX±CRTx	42	83	n.r.
Tinchon et al. (28)	Retrospective	12	BRPC	2010-2012	FOLFIRINOX	83	n.r.	n.r.
Dholakia et al. (66)	Retrospective	50	BRPC/LAPC	2007-2012	FOLFIRINOX or Cape or Gem or GemOx +RTx	58	93	23
Lee et al. (67)	Phase II	43	BRPC/LAPC	2006-2008	GemCape	39.5	82	23
Hosein et al. (27)	Retrospective	18	BRPC/LAPC	2008-2011	FOLFIRINOX +RTx	55.5	80	n.r.
Peddi et al. (68)	Retrospective	61	BRPC/LAPC/ metastatic	n.a.	FOLFIRINOX	35	n.r.	n.r.
Strobel et al. (69)	Retrospective	199	LAPC	2001-2009	5FU or Gem or Gem-based ±CRTx	47	30	n.r.
Katz et al. (70)	Retrospective	129	BRPC	2005-2012	Gem-based +CRTx	66	95	33
Arvold et al. (71)	Retrospective	70	BRPC/LAPC	2005-2009	Cape or 5FU ±RTx	20	n.r.	19
Sahora et al. (72)	Phase II	25	BRPC/LAPC	2001-2003	GemDocetaxel	32	87	16
Sahora et al. (73)	Phase II	33	BRPC/LAPC	2003-2006	GemOx	39	69	22

radiological response according to RECIST criteria (p=0.1) but Overall Survival for patients who showed CA19.9 decline was significantly longer compared to non-responders (25 vs 9.6 months, p=0.03). Resection was performed in 42% of patients with a R0 rate of 83%. Faris et at. (30) reported the experience of the Massachusetts General Hospital on 22 patients with LAPC; none of them showed progressive disease and 5 (23%) were finally resected with complete resection in each case. For those patients presenting unresectable disease at laparotomy the Authors decided to proceed with intraoperative radiation-therapy according to their own institution protocol. No overall survival was calculated. A multicenter study by Marthey et al. (31) exploring the use of FOLFIRINOX on 77 patients with either LAPC and metastatic disease reported tumor resection for 28 (36%) patients with 25 (89%) having complete resection. The Authors also reported a quite good toxicity profile with only 6% of treatment withdrawal because of tolerability problems.

Sadot and colleagues reported the results of FOLFIRINOX administration to LAPC patients at Memorial Sloan Kettering Cancer Center between 2010 and 2013 (32). 101 patients were treated. Additional chemoradiation was administered to 63 patients showing locally unresectable disease at completion of FOLFIRINOX induction. Progressive disease was detected in 26 patients (26%). Surgical exploration was attempted in 35 patients with resection being completed in 31 (31%). R0 resection rate was 55%. The median Overall Survival was not reached in the group undergoing tumor resection.

Until now the largest experience with FOLFIRINOX in LAPC has been presented by Hackert et al. (33) In this study 575 patients selected for surgical exploration following neoadjuvant treatment between 2001 and 2015 were analyzed. FOLFIRINOX was administered to 125 individuals. Successful resection was performed in 50.8% of the total amount of patients, with the highest resection rate and R0 rate found in the FOLFIRINOX group (60.8% vs 48% achieved with other treatments, p=0.011 and 40.8% vs 31.3%, p=0.048 respectively). Of note, the presence of metastasis was the reason for primarily unresectability in a considerable amount of individuals to which FOLFIRINOX was delivered (47.2%). Adjuvant chemotherapy was administered to around 70% of patients and the subsequent overall median survival was 15.3 months no influence of the type of preoperative regimen on the prognosis.

In their meta-analysis on the use of preoperative FOLFIRINOX in 253 patients with LAPC Petrelli et al. (74) calculated an overall resection rate of 42,3% (68.5% among BRPC patients and 26.1% among initially unresectable patients) with an overall R0 rate of 91% (93% and 86% respectively): in other words they found that FOLFIRINOX allowed 39.4% of patients diagnosed with a locally advanced disease to obtain a complete resection, rate that was greatly superior to that obtained with other regimens previously available (23). Nonetheless no information about survival could be inferred from the reviewed series.

Once again, in the setting of LAPC Suker et al. (75) calculated a resection rate after FOLFIRINOX of 25.9% (varying from 0% to 43% in different clinical series) with a complete resection in the 78.4% of cases (from 50% to 100%). The population in analysis was composed by 315 patients. These results were very similar to those presented by Rombouts et al. (76) in their review (resection rate 28%, R0 rate 77%). In the patient-level meta-analysis by Suker the median overall survival was 24.2 months and the median progression free survival was 15 months (75). Survival data were incomplete in the paper by Rombouts since the reported median overall survival of 24.9 months derived from a single study enrolling less than thirty patients (76). Interestingly in both reports 57% of patients received radiation therapy after FOLFIRINOX.

These data confirmed the effectiveness of the multi-agent chemotherapy based on FOLFIRINOX to achieve a potentially curative resection and encouraging progresses in prognosis. Anyway a substantial heterogeneity of results emerges from the studies included (i.e. resection rates varying from 29 to 85% for LAPC patients according to *Table 1*), which might be ascribed to the different selection of patients for surgery in term of performance status and resectability. In fact, after the administration of FOLFIRINOX it is proven the difficulty to distinguish neoplastic residuals from scar-like hypoperfused tissue in the pancreatic area at cross-sectional imaging. CT and MRI are 71% sensible and 58% specific in detecting vessel infiltration after neoadjuvant treatment. (77). Even long experienced pancreatic surgeons demonstrated to fail in recognizing viable cancer from FOLFIRINOX-induced fibrosis. In a study by Ferrone and colleagues (53) imaging of 40 patients who completed neoadjuvant treatment for BRPC and LAPC were revised by either a senior pancreatic surgeon who was blind to the treatment and a multidisciplinary tumor board. While the latter concluded for the absence of disease progression and candidated all patients for surgery, the former could recognize resectable disease in only 30%. Finally all patients underwent resection after FOLFIRINOX, with a R0

rate of 92% and significantly better pathologic results in terms of positive lymph nodes, lymphatic and perineural invasion compared to a cohort of patients undergone upfront surgery.

Similar results were noted by Dholakia et al (66): of 50 patients diagnosed with borderline resectable pancreatic cancer and treated with chemo-radio therapy (FOLFIRINOX or other regimens), 29 (52%) had successful resection with positive margins in only 2 cases (R0 rate 93%). Notably among them the great majority had shown a radiographically stable (80%) or even progressed (17%) vascular involvement at re-staging imaging. Median overall survival and progression free survival were longer for patients undergone resection compared to those who did not (22.9 vs 13 months and 16.6 vs 5,9 months respectively, $p<0.001$), letting the Authors assume that surgical resection should be attempted even when radiological response to neoadjuvant treatment seems partial or absent.

If FOLFIRINOX seems to be the most effective choice to achieve a secondary resection and best outcomes (78), much less trials have been conducted to investigate Gemcitabine plus Nab-Paclitaxel in the neoadjuvant setting. A recent Spanish retrospective series compared the administration of Gemcitabine plus Nab-Paclitaxel versus surgery first in 81 patients with either resectable disease and BRPC (40). Resection rate after neoadjuvant treatment was 68.8% (78.9% in the resectable group and 61.5% in BRPC group). Longer overall survival was detected for patients undergone neoadjuvant therapy before surgery (30.6 vs 22.1 months, $p=0.04$): in the primarily resectable group no difference was found between neoadjuvant treatment and upfront surgery (23.5 vs 24.8 months, $p>0.05$) while for BRPC patients neoadjuvant treatment provided an overt improvement in survival compared to surgery alone (43.6 vs 13.5 months, $p<0.001$).

In the experience by Itchins et al. (35) 50 of 85 patients with resectable and BRPC were administered Gemcitabine plus Nab-Paclitaxel as neoadjuvant therapy. Overall resection rate was 79% with R0 rate being 75%. No differences were found in survival rate between Gemcitabine plus Nab-Paclitaxel and gemcitabine alone or FOLFIRINOX group (mOS 23.0 vs 29.0 vs 25.9 moths respectively, log-ranked $p=0.92$), neither between neoadjuvant approach and upfront surgery (mOS 25.9 vs 26.9 months respectively, $p=0.58$).

As shown in *Table 1*, only three randomized clinical trials were concluded in recent years on neoadjuvant treatment.

The LAP07 clinical trial (48) was designed with two subsequent randomizations: first patients with LAPC were randomized to receive Gemcitabine alone or Gemcitabine plus Erlotinib; subsequently those who presented non-progressive disease were randomized to continue with the same treatment versus shifting to Capecitabine-based chemo-radiotherapy. Primary outcome was overall survival. This trial was stopped for futility since no survival benefit could be detected from chemo-radiation compared to chemotherapy alone in patients with controlled disease after 4 months of induction therapy.

In the setting of resectable disease two trials were conducted to assess the effectiveness of neoadjuvant chemo-radio-therapy over upfront surgery (51,52). Both were stopped early due to slow recruiting and not significant results.

What Current Guidelines Suggest

Multimodal treatment for non-metastatic pancreatic cancer is warranted depending on clinical stage and resectability. Definitions of resectable disease, BRPC and LAPC released in recent years allowed different study results to be compared and, finally, guidelines to be drafted. Nevertheless, recommendations are often based on retrospective analyses or extrapolations from randomized trials in metastatic patients.

For patients diagnosed with primarily resectable disease, surgical resection followed by adjuvant chemotherapy based on Gemcitabine with the addition of Capecitabine is recommended (79). Two large retrospective cohort studies based on the American National Cancer Data Base suggest that neoadjuvant treatment does not help patients with resectable disease as it

might do in more advanced disease (45,50). On the contrary, a retrospective analysis from the same national database focusing on early-stage disease only reported better complete resection rates and survival rates for those patients undergone preoperative treatment (47). Thus, preoperative therapy should be reasonably considered in resectable disease only for those selected patients presenting the highest risk of tumor spread even without radiological evidence of metastases (7) (i.e. high levels of Ca19.9, large primary tumor, highly symptomatic disease, so called biological criteria of unresectability).

For patients diagnosed with BRPC many institutions have embraced the use of neo-adjuvant chemotherapy opposed to immediate surgery to obtain better pathological response at subsequent resection. American NCCN guidelines and European ESMO guidelines support this practice (7, 80). Nevertheless, no randomized clinical trial has been conducted to ascertain the superiority of neoadjuvant chemotherapy over upfront surgery for BRPC.

Patients suffering for locally advanced unresectable disease must be referred to clinical oncologists to start systemic therapy right after histological confirmation. FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel are nowadays the first choice to increase the likelihood of complete resection, (7), with the former being usually reserved to patients fit for a more aggressive treatment. ASCO guidelines clearly state that no data is available to support one regimen over another (81). Other options including Gemcitabine monotherapy and Gemcitabine-based regimens should be considered in patients with sub-optimal performance status. (81) If local disease progression without metastatic spreading is detected after first-line induction chemotherapy, radiation therapy may be offered.

Conclusions

Pancreatic cancer is a hard clinical challenge. Tumor resection remains the only chance of cure. Thus, clear definition of primarily resectable and unresectable disease was needed among specialists to speak a common language worldwide. In recent years such definitions were released describing three clinical entities, namely resectable cancer, BRPC and LAPC. Neoadjuvant treatment has rapidly gained consensus among clinical oncologists and surgeons; it was demonstrated that conversion from unresectable to resectable disease could be reached in at least a quarter of patients, with the same chance to obtain a complete resection as for initially resectable patients (that is more than 8 times of 10). Since actual radiologic imaging cannot predict the real post-treatment down-staging, several Authors concluded that it is worthy to perform surgical exploration in those patients who do not show a clear evidence of tumor progression after neoadjuvant treatment completion. In order to reach radical resection, frozen section biopsies should be performed when any vascular involvement is strongly suspected and, if negative, resections and subsequent anastomoses should be attempted (53). Furthermore, several studies demonstrated that neoadjuvant treatments are quite well tolerated and do not increase the postoperative morbidity rate (33, 53, 54, 56, 57, 62, 82). Undeniably the introduction of FOLFIRINOX and Gemcitabine plus Nab-Paclitaxel regimens for metastatic disease has signed a watershed in the menagement of non-metastatic disease too. Nowadays they represent the first option in patients with good performance status not candidate to upfront surgery.

The present literature review shows that several critical points still remain. The main limitation is that most of the studied presented are retrospective and included only a small number of patients. They often represent limited experiences of single institutions, with researchers adopting subjective criteria to determine the assignation to a neoadjuvant protocol. Therefore, conclusions cannot be generalized and, most of all, results in term of survival cannot be compared.

In addition *Table 1* clearly demonstrates the plethora of different drugs and schedules tested until now. According to the present review of the literature, FOLFIRINOX is the regimen most commonly adopted in recent years and it is also the first choice recommended by international guidelines along

with Gemcitabine plus Nab-Paclitaxel.

Radiation therapy, with or without chemotherapeutic sensitizers, was often used in addition to systemic therapy, with the doses and the schedules of treatment being the most variable. As for neoadjuvant chemotherapy, the best approach is yet to be defined. Promising results might be came from advancements in radiotherapy techniques, such as stereotactic body or hypo-fractionated radiation therapy.

If on one hand the large variety of chemo and radio-therapy approaches adopted in literature is a great limit to overcome, on the other side it shows a trend to the acceptation of neoadjuvant treatment worldwide. What was a promising strategy up to a few years ago, it is now a current standard of care for unresectable pancreatic cancer, whom effectiveness is not under discussion. To what extent these successes could effectively stand is still unknown. Therefore, results of ongoing randomized clinical trials are strongly needed to definitively support this approach and, most of all, define the best protocols to gain significant improvements in prognosis.

Conflict of Interests

The authors declare no conflict of interests.

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