Neoadjuvant FOLFIRINOX followed by gemcitabine based chemoradiation as a treatment paradigm for Borderline resectable pancreatic adenocarcinoma

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INTRODUCTION

Carcinoma of the pancreas is a lethal malignancy [1-3]. Over the last few decades, it has a markedly increased incidence and ranked as the 7th leading cause of cancer-related deaths [4]. In the United States, the estimated newly reported cases and deaths from pancreatic cancer were about 55,440 and 44,330 respectively, in 2018 [5]. Cancer of the exocrine pancreas has been traditionally associated with low resectability [6-9]. Poor prognosis [2, 3,10,11], rarely curable and has a 5-year overall survival rate of 8% and a 10-year Overall Survival (OS) of 3% for all the stages [2,12]. Improvements in imaging technology, including positron emission tomographic scans, endoscopic ultrasound examination, magnetic resonance imaging scans, spiral computed tomographic scans, and laparoscopic staging can help to diagnose and identify patients with diseases that are not prone to resection [2, 7, 10, 13].

Patients with pancreatic cancer, at any stage, would be considered as appropriate candidates for the clinical trials, due to the well documented inadequate response to the conventionally used therapeutic modalities including radiation therapy, surgery, and chemotherapy [1, 3, 6, 7, 12, 14].

Patients with Borderline Resectable Pancreatic Cancer (BRPC) and locally advanced unresectable pancreatic cancers are anatomically characterized by the involvement extent of major vessels, which is likely associated with positive resection margin [15]. Several clinical trials have proposed that preoperative chemoradiotherapy for potentially resectable tumours helps to improve local recurrence and survival in resected patients [1, 7, 12, 13]. The 5-year OS was (20%) for patients undergoing resection, which may be improved up to (32%) in patients achieving complete resection and (40%) in those with node-negative disease [12]. Thus, if the tumour is actually localized to the pancreas, the highest cure rate is recorded; however, unfortunately, only less than (20%) of patients are at this stage of the disease [14].

Several studies have recommended preoperative chemoradiotherapy for the locally advanced tumours, that were subsequently could be resected [1, 10, 12,13,16].

Previously, in a multi-institutional phase 2 study that was conducted on patients with pancreatic cancer to evaluate the
neoadjuvant oxaliplatin and gemcitabine together with radiation therapy in patients with pancreatic cancer. They reported a resection rate of 63% for all treated patients, with 53% for R0 resections. Kim and his colleagues reported median survival of (18.2) months for all patients and (27.1) months, for resected patients [15].

Recently, In 2020, in the phase 2 trial on patients with (BRPC), neoadjuvant FOLFIRINOX and Intensity-Modulated Radiation Therapy (IMRT) concurrent with fixed-dose/rate gemcitabine, significantly improved the median OS for resected patients, with a median value of (37.1) months [13].

There was an amazing improvement in the magnitude of median OS, but it came with a price. Notably, there was an increased exposure and duration to local therapy intensification and systemic treatment [13]. However, the clinical evidence of significant activity in (BRPC) stimulated us to conduct this exploratory study. In this study, we investigate the efficacy of neoadjuvant FOLFIRINOX followed by gemcitabine when used concurrently with IMRT external beam radiotherapy as first-line therapy in (BRPC) patients.

PATIENTS AND METHODS

Patient Eligibility Criteria

This phase II trial was carried out from January (2017) to January (2020). Twenty-three chemotherapy and radiotherapy-naïve patients with, confirmed measurable (BRPC) (BRPC stage has (2020). Twenty-three chemotherapy and radiotherapy-naïve patients with, confirmed measurable (BRPC) (BRPC stage has

Inclusion criteria

Includes Chemotherapy/radiotherapy-naïve, (18-70) years old patients; Eastern Cooperative Oncology Group (ECOG) performance status of (0-1); measurable borderline resectable disease; adequate bone marrow reserve (WBC count ≥3.5 × 10^9/L, ANC count ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, and haemoglobin ≥ 10 g/dL), preserved renal functions (creatinine clearance ≥ 60 mL/min) and preserved liver functions (transaminases< (2) × upper normal limit, and serum bilirubin level< (1.5) mg/dL).

Exclusion criteria

Includes symptomatic heart failure, severe arrhythmia, peripheral neuropathy, prior chemotherapy or radiotherapy, pregnant or lactating mothers, active infection, previous history of hypersensitivity reactions, any other uncontrolled medical problems or other malignancy.

Design of the study

This is a single-arm prospective (phase II) study of a single institution. Protocol approval was given by the Ethics Committee. Prior to initiation of any treatment; an informed consent was signed by all patients.

Pre-treatment evaluation

Pre/on-treatment close monitoring consisted of detailed medical history, physical examination, routine laboratory studies, pelvic and abdominal ultrasound, CT-scan of the pelvis, abdomen, and chest and (CA19.9 and CEA) measurement. Prior treatment, histologic, or cytological evidence of the pancreatic adenocarcinoma was documented in all patients.

Treatment plan and dose modification

Eligible patients received biweekly FOLFIRINOX (oxaliplatin (85) mg/m^2 given as a 2-hour intravenous IV infusion, followed immediately by leucovorin 400 mg per square meter, given as a 2-hour IV infusion, with the addition, after 30 minutes, of irinotecan 180 mg per square meter, administer as a 90-minute IV infusion was followed immediately by fluorouracil 400 mg per square meter, administered by IV bolus, followed by a continuous IV infusion of 2400 mg per square meter over 46 hours, repeated every 2 weeks for 6 months of chemotherapy).

Patients without Progressive Disease (PD) or unacceptable toxicity continued treatment up to 12 times over 6 months. Adequate hydration, anti-emetic therapy as well as steroids were secured for all patients. Antibiotics and growth factors, as a granulocyte-colony stimulating factor (G-CSF), were given to patients, guided by their continuous clinical evaluation.

Dose adjustment of FOLFIRINOX

Decisions were taken biweekly to modify the doses of chemotherapy, withhold treatment or progress with the schedule. Full biweekly doses of FOLFIRINOX regimen were given only if the absolute granulocyte count (AGC) was >1,000 cells/µl, platelets were > 100,000 cells/µl, and non-hematologic toxicities were ≤ grade 2. If the AGC ranged between (500-1,000) cells/µl or the platelet count ranged between (50,000-100,000) cells/µl, the FOLFIRINOX regimen dose was reduced by 25%. FOLFIRINOX regimen dose was reduced by 50% for grade 3 non-hematologic toxic effects. If the AGC was <500 cells/µl, the platelet count was ≤ 50,000 cells/µl and/or the non-hematologic toxic effects was grade 4, the FOLFIRINOX regimen dose was withheld, and the patient was reevaluated the following week.

Radiotherapy and gemcitabine administration

After 6 months of FOLFIRINOX, protocol-based concurrent gemcitabine IMRT external beam radiation therapy was delivered at 2.0 Gy per fraction, to a total dose of the mean planning target volume of 50.0 Gy if possible, in 25 fractions. Gemcitabine was administered on days 1, 8, 22, and 29 (1000 mg/m² infused over 100 minutes).

Patients were treated with IMRT external beam radiation therapy. The radiotherapy field for IMRT encompassed the
The primary endpoint of this study was R0 resection rates, (as defined by the absence of both microscopic/gross involvements of tumour resection margins) in (BRPC) population. Secondary endpoints were the overall response rate, OS, progression-free survival and toxicity. Disease progression was assessed from the first chemotherapy dose, and it was defined as increase in the size of a previously present disorder as documented by serial axial CT, the appearance of new local/distant metastatic disorder.

Statistical analysis

Twenty-three patients were enrolled in the current study between January 2017 and January 2020. The date of this analysis was June 2021.

OS rates were calculated, by the Kaplan-Meier method [19], from the start of biweekly FOLFIRINOX to the time of the last follow-up visit or death, using SPSS (Statistical package, version 21.0). Progression-free survival was the time elapsed from the initiation date of biweekly FOLFIRINOX to the date of the first evidence of disorder progression or death in the absence of disease progression. OS and progression-free survival were compared by the Kaplan-Meier method [19] with statistical significance evaluated by the log-rank test. Mean and Standard Deviation (SD) were calculated from quantitative data. All P values were two-tailed; a value of ≤ 0.05 was considered significant.

RESULTS

Patient characteristics

Patient characteristics were listed in Table 1. The median age was 53 years (range, 36-68). Fourteen patients (60.8%) had performance status 1. Twelve patients (52.2%) had involved body and tail pancreatic sites. Three (13.1%) patients had a biliary stent. The median level of CA19.9 was 600 U/ml. The median age was 53 years (range, 36-68). Fourteen patients (60.8%) had performance status 1. Twelve patients (52.2%) had involved body and tail pancreatic sites. Three (13.1%) patients had a biliary stent. The median level of CA19.9 was 600 U/ml. The median maximum cross-sectional Tumour Area (TA) was 8.7 cm².

Treatment administration

A total of 114 FOLFIRINOX chemotherapy cycles were administered. Patients were treated with a median number of 4 cycles of FOLFIRINOX (range 3-6 cycles), with dose modifications (according to criteria of dose adjustment mentioned previously in patients and methods) in 48.2% (55/114) of all FOLFIRINOX cycles.

Four patients (17.4%) had >3 dose delay of gemcitabine during concurrent gemcitabine-IMRT external beam radiation therapy. Two (9%) patients had radiotherapy interruptions due to toxicity. Fifteen patients (65.2%) complete 2 cycles of gemcitabine post radiation therapy.

Patients’ response to this regimen

The overall response rate (CR+PR) was 43.5% (10/23) of all patients and the disease control rate (CR+PR+SD) was 82.1% (19 patients). Nine patients (39.1%) had stable disease and 4 patients (17.4%) had disease progression (Table 2).
Pancreatic resection

Fourteen (60.9%) of the 23 patients who received this treatment protocol were thought to be candidates for pancreatic resection (either pancreaticoduodenectomy or distal pancreatectomy) based on CT images obtained four weeks after chemoradiation completion. The pre/post-treatment CT scans were reviewed to evaluate the lesion size and its relationship with the vessels before considering surgery. The resection rate in all treated patients was (60.9%), with R0 resections in 10 patients (43.5%). The median number of dissected regional lymph nodes was 10 (range, 5-15), and 9 patients (39.1%) had a positive metastatic nodal disease. No surgery-related mortality was reported.

Survival

All our patients had a regular follow-up, with no one having lost follow-up in the current study. The median follow-up period was 24.5 months ± SE 1.01.

Median (OS) for all our patients was 23 months ± SE 8.451, (95% CI, 6.437-39.563) (Figure 1). The 1-year and 2-year OS rates for all our patients were 74.7% and 49.6% respectively (Figure 1). It was 13 months ± SE 2.336, (95% CI, 8.421-17.579) for unresected patients and 30 months (95% CI, not reached) for resected patients (Figure 2).

Median Progression-Free Survival (PFS) for all our patients was 16.000 months ± SE ± 4.440), (95% CI, 7.297-24.703) (Figure 3). The 1-year and 2-year PFS rate was 54.9% and
35.3% respectively, (Figure 3). It was 10.000 months, SE ± 2.942 (95% CI, 4.233-15.767) for unresected patients, and 20 months, ± 2.828 (95% CI, 14.456-25.544) for resected patients (Figure 4).

**Toxicity**

To assess non-hematologic/hematologic toxicities (Table 3), all enrolled patients were evaluated for toxicity and adverse events by the common terminology criteria for adverse event version 3.0; NCI-CTC [18]. The most common grades (3-4) haematological toxicities were neutropenia in 10 patients (43.5%), with two patients (8.7%) suffering from febrile neutropenia, and another two patients (8.7%) developed grade (3-4) thrombocytopenia. Grade (3-4) diarrhoea in 4 patients (17.4%), nausea in 9 patients (39.1%) and mucositis in 2 patients (8.7%) were the most common Grade (3-4) non-haematological toxicity. Eight patients (34.8%) were started on prophylactic G-CSF concomitant with the first FOLFIRINOX cycle while additional nine patients (39.1%) had G-CSF support, which was added in later FOLFIRINOX cycles.

Four patients (17.4%) had >3 dose delay of gemcitabine during concurrent gemcitabine-IMRT external beam radiation therapy, and 2 (8.7%) patients presented with gastrointestinal bleeding with evidence of duodenal or gastric ulceration. Two (8.7%) patients had radiotherapy interruptions due to toxicity.

Due to treatment-related toxicity, ten (43.5%) of the 23 patients treated with this regimen were admitted to the hospital for

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<th>Tab.3. Hematologic and non-hematologic grade 3 and 4 toxicity of this regimen in the management of the 23 patients with borderline resectable pancreatic cancer</th>
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<td><strong>Enrolled patients</strong></td>
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<td><strong>Haematologic Toxicity</strong></td>
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supportive care. The median stay was 4 days. Five of these 10 patients were admitted twice and 5 were admitted three times.

**Late toxicity**

Two episodes (8.7%) of severe late effects that might have been treatment-related occurred. The 2 patients had episodes of duodenal ulceration with bleeding. An endoscopic biopsy was negative for the tumour but showed severe reactive changes consistent with the impact of treatment.

**DISCUSSION**

Pancreatic cancer management remains a daunting challenge, often requiring a multidisciplinary approach to provide an efficient approach and, preferably, to optimise survival. The combination of local-regional approaches, such as surgery and radiotherapy, and systemic micrometastasis eradication therapies should also be considered for (BRPC) patients and those with locally advanced, unresectable disease [1,2,6].

BRPC has a poor prognosis with upfront surgery due to the high likelihood of microscopic and/or macroscopic residual tumours [20,21]. However, neoadjuvant therapy may lead to improvement in R0 resection rates and long-term survival [7].

The integration of gemcitabine with radiation in a combined modality regimen may represent one strategy to improve outcomes in patients with pancreatic cancer, considering its activity as a single agent and laboratory studies that have demonstrated potent radiosensitization in human pancreatic cancer cell lines [12,13,15,16,22].

FOLFIRINOX is clinically beneficial in both metastatic and non-metastatic pancreatic cancer patients, considering substantial rates of adverse effects and the use of dose modifications. The toxicity of the regimen did not distort overall response and survival [23-26]. In our institution, it is the standard systemic treatment for metastatic, BRPC and locally advanced disease in patients with good performance status.

These observations have led us to document the use of neoadjuvant FOLFIRINOX and gemcitabine-based chemoradiation and its efficacy and tolerance in BRPC patients.

Our treatment schedule was based on data from Tran, et al. study that concluded that the optimal therapeutic index, in BRPC patients, can be achieved with FOLFIRINOX administration followed by gemcitabine-based chemoradiation [13].

In our study, responses were observed in 43.5% (10/23) of patients which were similar to the results of the Tran, et al. study [13], in patients with BRPC published in 2020 (RR was 44%) [13]. However, our results were better than the results of a study carried out between May 2016 and March 2018, in which investigators at Asan Medical Center, Seoul, Korea treated 44 patients with BRPC with neoadjuvant modified FOLFIRINOX followed by postoperative gemcitabine [7] who developed response rates of 34.1%.

In the current study, the disease control rate (PR+CR+SD) of 82.1% (19 patients) was comparable to the results of the Tran, et al. trial on FOLFIRINOX followed by gemcitabine-based chemoradiation in (BRPC) (disease control rate of 88%) [13].

In retrospect, it is now obvious from clinical data that when gemcitabine is used simultaneously with radiotherapy, the size of irradiated normal tissue is a crucial variable. The recommended dose of 1000 mg/m² infused over 100 minutes on days 1, 8, 22, and 29 that we used with 50 Gy in 25 fractions to regional radiotherapy fields to most of the patients in our study is comparable to the dose given in prior study that used IMRT irradiation concurrently with gemcitabine [13]. While Sakamoto, et al. [27], suggest that because of its decreased toxicity, the low-dose gemcitabine infusion regimen can be consistently administered to patients with both locally advanced and systemically spreading pancreatic cancer, resulting in better life quality and an improved safety profile compared with the current care regimen for infusion.

The infusion rate of gemcitabine is a significant variable which has become evident from clinical data. Most studies assessing concomitant radiotherapy and gemcitabine were given at the manufacturer’s recommended 30-minute as infusion rate for gemcitabine [28], which may not be ideal based on other clinical studies suggesting that a 10 mg/m²/min infusion rate is more efficient [13,16,29,30]. The rate of infusion we used could have been serendipitously optimal; however, the smaller radiation volume with the use of IMRT is probably more important and could, in part, explain why we can be able to use higher doses of gemcitabine with good tolerability with the ability to finish gemcitabine-based chemoradiation for all our patients.

It is now obvious that the fractionation/volume of irradiated normal tissue affects the patients’ tolerance with concomitant gemcitabine [1-3]. Omitting elective nodal irradiation is an obvious means of expanding the therapeutic ratio in the studies of concomitant gemcitabine and radiotherapy. This idea has been advocated by researchers at the University of Michigan in patients with irresectable diseases 30 and owing to the enhanced toxicity associated with elective nodal irradiation if gemcitabine is to be used in radiotherapy; it tends to be the most desirable technique. The objective progression rate of the primary tumour was so high, in patients receiving concurrent radiotherapy and gemcitabine, in their study of BRPC patients. Indeed, it is hard to believe that elective nodal irradiation may have been of any benefit. In our study, higher doses of the weekly administered gemcitabine have been tolerated as radiotherapy is delivered to gross disease and involved regional lymph nodes only by the use of IMRT.

Our patients who received neoadjuvant FOLFIRINOX followed by gemcitabine-based chemoradiation were selected carefully (the ECOG PS was ≤ 1, with 39.1% of patients having ECOG PS of 0), yet the rate of hospitalization was elevated due to frequently reported severe acute toxicity. Ten (43.5%) of the 23 patients treated with the current regimen were admitted to the hospital for supportive care due to treatment-associated toxicity, with a median stay period of 4 days. Five of these 10 patients were admitted twice, while 5 patients were admitted three times. Our rate of hospitalization for treatment-related toxicity was higher than the rate of hospitalizations due to adverse events in Peddi, et al. trial (34.4%) [26] and comparable with Paris, et al. trial
were treated with FOLFIRINOX, at their institution between
in a full dose, due to its toxicity profile [34]. A retrospective
have noted that oncologists were hesitant to use FOLFIRINOX,
cycles in response to adverse events. Researchers at Yale University
In our study, the dose was modified in 48.2% (55/114) of all
(17.4%), were the most common Grade 3-4 non-haematological
3-4 nausea in 9 patients (39.1%) and diarrhoea in 4 patients
neutropenia in the FOLFIRINOX group in the ACCORD trial
[33], while, there was no treatment-related death in our study.
Washington University physicians used a database to track the
FOLFIRINOX efficacy and tolerance [32]. 48% of patients
starting with the first cycle were given prophylactic growth factor
support; 10% of patients started (G-CSF) in the subsequent
cycles. Neutropenia (grades 3 and 4) has been reported in a
lower proportion of patients (14%) [32]. Differences in rates
of grades 3 and 4 neutropenia between our trial and other trials
may be due to the variations in the number of patients in all
these studies, the varying stages of included pancreatic cancers
as well as the differences in the regimens of FOLFIRINOX-
base treatment.

The severe non-haematologic toxicity rate in the present study
was similar in patients treated with neoadjuvant FOLFIRINOX
followed by gemcitabine-based chemoradiation and in those
treated with the same regimen in Tran, et al. [13] study. Grade
3-4 nausea in 9 patients (39.1%) and diarrhoea in 4 patients
(17.4%), were the most common Grade 3-4 non-haematological
toxicity in our study. Similarly, the most frequently reported
non-hematologic treatment-related adverse events in Tran, et al.
trial [13] were nausea and vomiting in 40% and diarrhoea in
16%.

In our study, the dose was modified in 48.2% (55/114) of all
cycles in response to adverse events. Researchers at Yale University
have noted that oncologists were hesitant to use FOLFIRINOX,
in a full dose, due to its toxicity profile [34]. A retrospective
study has been conducted on pancreatic cancer patients, who
were treated with FOLFIRINOX, at their institution between
June (2010) and June (2011), to evaluate the possible effect of
dose reduction on efficacy/toxicity. In the first cycle, only 17%
of patients received a complete dose of FOLFIRINOX. The
median relative doses of oxaliplatin, irinotecan, 5-FU bolus, and
5-FU infusion were 90%, 68%, 68%, and 100%, respectively.
To track the tolerance and efficacy of FOLFIRINOX, Peddi, et al.
used a registry [32]. In the majority of patients, the protocol
was empirically altered because of concern about possible
toxicities. In 48%, the 5-FU bolus was deleted. In 46%, the
dosage of Irinotecan was reduced.

In our study, the median (OS) for all our patients was 23
months similar to that published in many other trials, in which
the median OS of their population was in the range of 21.7-
37.7 months [13, 24, 25]. In the current study, the 1-year and
2-year OS rates for all our patients were 74.7% and 49.6%
respectively, compared with the 75.4% and 54.2%, respectively
reported in the Tran, et al. trial [13].

The median OS survival reported in patients with the unresectable
disorder, who were treated with this combination was similar to
OS rate in patients treated with the same regimen in Tran, et al.
[13] study; (13 months vs. 12.6 months respectively). These
observations concluded a very narrow therapeutic index for the
utility of neoadjuvant FOLFIRINOX followed by concurrent
gemcitabine and radiotherapy administered in this way without
malignant resection. In spite of the reported increased toxicity no
clear significant increase in efficacy in patients not amenable
for curative surgery. However, the OS of the resected cohort
was more favourable. In our study, the median OS of the R0
resected patients is 30 months, approximately comparable to
that mentioned in R0 resected patients of other studies treated
with preoperative FOLFIRINOX followed by chemoradiation
for BRPC [13,24,25].

Because curative therapeutic approaches in pancreatic cancer
patients must include surgery, all therapies that increase
resectability are of interest. A possible benefit of FOLFIRINOX
followed by concurrent gemcitabine and radiotherapy in this
study was the ability to perform surgery in 14 patients
(60.9%) of (BRPC) patients. Ten patients (43.5%) receiving
FOLFIRINOX followed by concurrent gemcitabine and
IMRT external beam radiotherapy underwent margin negative
pancreaticoduodenectomies.

The R0 resection rate in this study was observed to be 43.5%
which is lower than the 52% mentioned in Tran, et al. [13]
study using the same regimen of our study (FOLFIRINOX
followed by concurrent gemcitabine and radiotherapy) and the
64% published in Katz, et al. phase 2, a multi-institutional trial
using FOLFIRINOX followed by gemcitabine concurrently
with radiation in patients with BRPC [24] as well as the 65%
R0 resection rate in Murphy, et al. using FOLFIRINOX
followed by capectabine concurrent with radiation in patients
with (BRPC) [25]. However, this 43.5% R0 resection rate
in our study was observed to be better than the R0 resection
Differences in resection rates between our trial and other trials
may be due to the small number of patients in all these studies,
the varying definitions of (BRPC) as well as the variations in
the experience of the surgeons.
REFERENCES


According to the results achieved with FOLFIRINOX followed by gemcitabine and 50 Gy IMRT, both local and distant failure rates were significant problems in our patients, regardless of the used chemotherapy. Although the FOLFIRINOX followed by a combination of radiation and gemcitabine, is a potent cytotoxic intervention modality [22], we reported one-year and two-year PFS rates of 53% and 30% respectively. Median (PFS) for all our patients was 16 months, slightly more than the 13.1 months reported in the Tran et al [13] study using the same regimen of our study (FOLFIRINOX followed by concurrent gemcitabine and IMRT radiotherapy). We have used a radiotherapy dose of 50 Gy in 25 fractions. However, some may argue that higher radiation doses may be more appropriate for unresectable diseases with enhanced survival, but there is no compelling proof up till now [37]. In our experience, distant metastasis is the predominant cause of death. Thus, distant metastases are still the main limitation. This clarifies the need for ongoing research into novel systemic agents for this disease [38-40]. Thus far, major improvement in outcome for patients with BRPC has not been demonstrated with this therapy. The study of the impact of higher radiation doses does not seem to be a priority until more reliable systemic therapy is developed.

CONCLUSION

In conclusion, the FOLFIRINOX followed by concurrent gemcitabine and IMRT external beam radiotherapy regimen has gained increased acceptance due to its better efficacy as first-line therapy in patients with BRPC, improved response rate and median OS over that achieved with gemcitabine-based combination regimens in previous studies. The doses and schedules of concurrent gemcitabine and radiotherapy used in this study had a high toxicity rate than did treatment with other multiagent combinations including, gemcitabine and nab-paclitaxel and radiotherapy [41]. Thus, in spite of, the overall survival rate was significantly better for patients who received neoadjuvant FOLFIRINOX followed by concurrent gemcitabine and radiotherapy, this treatment program still has significant limitations. Considering the toxicity and efficacy, this regimen could be a viable therapeutic option in selected patients with a good PS only.

Further prospective trials should evaluate how to adjust doses to ameliorate the toxicity of this regimen. In addition, patients with BRPC should continue to be enrolled in prospective trials to explore potential formulations of concomitant radiotherapy with cytotoxic agents and/or biologic agents. Future prospective research should also be supported based on further knowledge of tumour biology, targeting different growth factor signalling pathways, and developing new technologies, including the discovery of biomarkers that predict the response to treatment.

DISCLOSURE STATEMENT

No potential conflict of interest was documented by the author(s).


